

# ACTA PÆDIATRICA

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## REDACTORES:

IN DANIA: C. E. BLOCH, KØBENHAVN. IN FENNIA: ARVO YLPPÖ, HELSINGFORS. IN HOLLANDIA: E. GORTER, LEIDEN, CORNELIA DE LANGE, AMSTERDAM, J. VAN LOOKEREN CAMPAGNE, GRONINGEN. IN NORVEGIA: TH. FRÖLICH, OSLO. IN SUECIA: I. JUNDELL, STOCKHOLM, A. LICHTENSTEIN, STOCKHOLM, WILH. WERNSTEDT, STOCKHOLM.

EDITOR: I. JUNDELL, STOCKHOLM

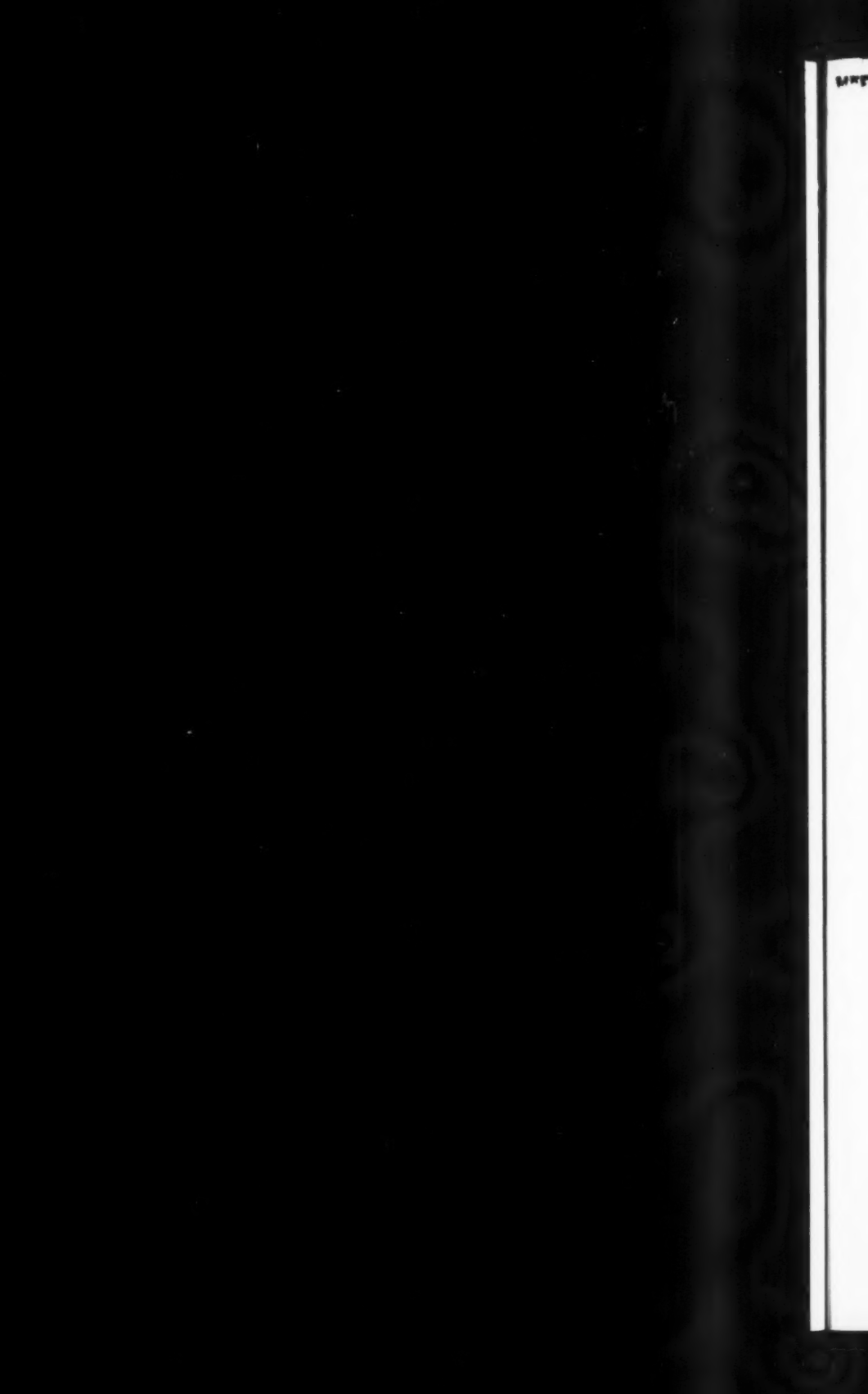
Vol. XXXII.

MCMXLIV—MCMXLV

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*Almqvist & Wiksells Boktryckeri Aktiebolag*  
UPPSALA 1944—1945





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IN DANIA: C. E. BLOCH, KOBENHAVN, S. MONRAD,  
KOBENHAVN. IN FENNIA: ARVO YLPPÖ, HEL-  
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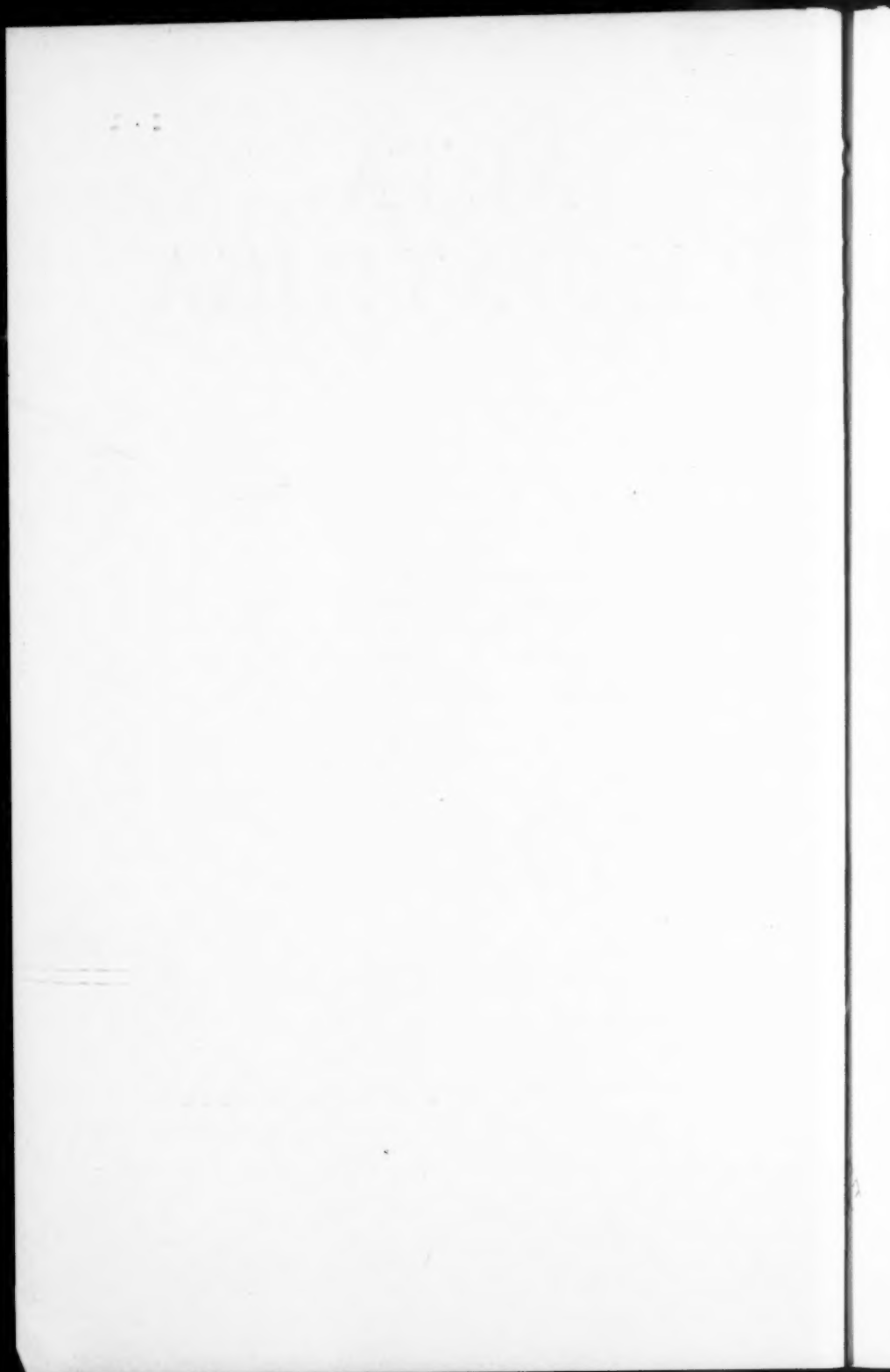
EDITOR I. JUNDELL, STOCKHOLM

Vol. XXXII. Fasc. 1

30: IX. 1944

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*Almqvist & Wiksells Boktryckeri Aktiebolag*  
UPPSALA 1944



## Über die Zusammensetzung und besonders den Fettgehalt der Muttermilch mit Rücksicht auf die Ernährungslage der Kriegszeit.

Von

T. SALMI.

Der wichtigste Bestandteil der Milch ist vom kalorimetrischen Standpunkt aus betrachtet das Fett; gleichzeitig erweist sich aber auch das Fett, was seine Menge anbetrifft, als ihr unbeständigster Teilstoff. So werden für den Fettgehalt der Muttermilch Grenzwerte von 0,76—9,05 % genannt, während der Gehalt an Eiweiss nur von 1,09 %—1,90 %, der Gehalt an Zucker von 2,94 %—7,20 % und der Aschenbestand von 0,10 %—0,41 % schwanken soll. Die grosse Unbeständigkeit des Fettgehaltes wird u. a. auch durch die tägliche, von Kinderärzten gemachte Erfahrung erwiesen, dass nicht selten von einem Kinde zur Deckung seines Kalorienbedarfes Brustmilch der eigenen Mutter in geringerer Menge gefordert wird, als Milch einer andern Mutter. Diese Tatsache lässt sich beinahe ausschliesslich durch die Verschiedenheit des Fettgehaltes der Milch der einzelnen Mütter erklären. Ganz allgemein ist die Ansicht verbreitet, dass auf den Fettgehalt der Muttermilch ausser der Individualität auch die Rasse der Mutter einen Einfluss hat. Auch YLPPÖ hat feststellen können, dass die Milch der finnischen Mutter bedeutend fettreicher ist als die der deutschen. Als auf den Fettgehalt der Muttermilch einwirkende Faktoren werden ausserdem die Kost der stillenden Mutter, die Dauer der jeweiligen Mahlzeiten sowie auch die Tageszeit, die Menge der abgesonderten Milch u. a. m. genannt;

auch soll die Milch der verschiedenen Phasen eines Stillaktes verschieden hohen Fettgehalt zeigen.

In den vorliegenden Untersuchungen wurde die Aufmerksamkeit der Höhe des Fettgehaltes der Muttermilch und einigen sie beeinflussenden Faktoren zugewandt; dabei ist das Augenmerk speziell auf die durch die Kriegszeit bedingten besonderen Verhältnisse gerichtet worden. Das dazu verwandte Material umfasst Milchspenderinnen der Muttermilchzentrale Helsinki des Mannerheim-Verbandes und ist auf zwei Gruppen verteilt: die erste umfasst die Milchspenderinnen des Jahres 1939, insgesamt 68 Mütter, während in die zweite insgesamt 130 Mütter aus den Jahren 1941—1942 gehören. Der Fettgehalt wurde nach dem Verfahren von GERBER für die ganze Tagesmischmilch jeder einzelnen Mutter bestimmt. Wie die folgenden, von sechs Müttern zwecks Erhalt eindeutiger Resultate genommenen Individualproben zeigen, ist der Fettgehalt der Milch sowohl während der einzelnen Phasen desselben Abmelkens, wie auch zu den verschiedenen Tageszeiten bedeutenden Schwankungen unterworfen.

	I	II	III	IV	V	VI
	6 Uhr	6 Uhr	6 Uhr	6 Uhr	6 Uhr	6 Uhr
Beim Anfangsmelken .	0,5 %	0,8 %	1,0 %	1,4 %	0,6 %	1,0 %
Mittel- » .	1,5 »	2,4 »	2,3 »	2,5 »	2,8 »	3,2 »
End- » .	2,9 »	5,0 »	7,4 »	2,9 »	4,8 »	3,5 »
Mittelwert . . .	1,6 »	2,7 »	3,6 »	2,8 »	2,6 »	2,6 »
	10 Uhr	10 Uhr	10 Uhr	10 Uhr	10 Uhr	10 Uhr
Anfangsmelken .	3,6 %	1,2 %	2,1 %	2,5 %	2,1 %	0,6 %
Mittel- » .	4,8 »	2,3 »	3,6 »	3,8 »	4,5 »	3,6 »
End- » .	5,2 »	5,4 »	7,5 »	4,2 »	5,8 »	5,4 »
Mittelwert . . .	4,5 »	2,9 »	4,4 »	3,5 »	4,1 »	3,2 »
	14 Uhr	14 Uhr	14 Uhr	14 Uhr	14 Uhr	14 Uhr
Anfangsmelken .	2,7 %	1,3 %	1,2 %	2,6 %	1,7 %	0,7 %
Mittel- » .	4,1 »	4,3 »	3,5 »	3,3 »	4,1 »	4,6 »
End- » .	4,9 »	4,8 »	7,2 »	3,1 »	6,1 »	5,2 »
Mittelwert . . .	3,9 »	3,8 »	3,9 »	2,9 »	3,9 »	3,5 »

	I	II	III	IV	V	VI
	18 Uhr	18 Uhr	18 Uhr	18 Uhr	18 Uhr	18 Uhr
Anfangsmelken .	0,6 %	1,4 %	1,4 %	1,6 %	0,8 %	0,8 %
Mittel- » .	2,9 »	3,4 »	3,5 »	2,8 »	3,0 »	3,0 »
End- » .	4,1 »	3,9 »	7,5 »	3,2 »	4,0 »	3,5 »
Mittelwert . .	2,5 »	2,9 »	4,1 »	2,4 »	2,6 »	2,4 »

	22 Uhr	22 Uhr	22 Uhr	22 Uhr	22 Uhr	22 Uhr
Anfangsmelken .	2,2 %	1,1 %	1,1 %	2,2 %	0,9 %	0,8 %
Mittel- » .	3,3 »	3,0 »	2,6 »	2,5 »	3,6 »	3,1 »
End- » .	3,4 »	3,3 »	6,6 »	3,8 »	4,2 »	3,5 »
Mittelwert . .	2,9 »	2,4 »	3,4 »	2,8 »	2,9 »	2,5 »

Aus der Tabelle geht also hervor, dass in jedem einzelnen Falle der Fettgehalt der Milch während des sog. Anfangsmelkens, worunter die während der ersten 2—3 Minuten erhaltene Milch zu verstehen ist, am niedrigsten, während er beim End-Abmelken beinahe in allen Fällen am höchsten war. Während des Mittel-Melkens liegen die Werte zwischen den beiden erstgenannten und dabei in den meisten Fällen in der Nähe der für die ganze Melkzeit errechneten Mittelwerte. COCCHERI und andere haben auch festgestellt, dass der Fettgehalt der Milch am höchsten zum Ende des Abmelkens und gewöhnlich sogar drei Mal so hoch wie der Fettgehalt der Anfangsmilch ist. Nach LUCIGNANI soll in der dritten 5 Minuten-Phase des Abmelkens der Fettgehalt gleich hoch wie der Mittelwert der Fettmenge für die ganze Melkzeit sein, weswegen die Milch dieser Phase auch gut zur Probeabnahme geeignet wäre. WIDDOVS und LOWENFELD dagegen sind der Ansicht, dass der Fettgehalt jeder einzelnen Milchprobe sowohl von der jeweiligen in der Brust vorhandenen Milchmenge — je mehr Milch um so weniger Fett — wie auch von dem an die Brustdrüse angesetzten Druck abhängig sei. Die geringsten Mengen Fett findet man in den spontan hervorquellenden Milchtropfen.

*Die fettreichste Milch ist in unseren Fällen um 10 Uhr (Fälle I, III, IV, V) und um 14 Uhr (Fälle II, VI) festgestellt*

worden. Denselben Befund haben auch viele deutsche Forscher, u. a. CZERNY und KELLER erhoben. Die fettärmste Milch hingegen ist entweder am Abend oder auch am frühen Morgen anzutreffen. Diese Beobachtung hat ausser vielen anderen Forschern, u. a. auch DEEM gemacht. RUŽIČ hat dagegen als seine Ansicht ausgesprochen, dass die Tagesschwankungen im Fettgehalt der Milch nicht einer von der Natur bedingten Gesetzmässigkeit unterworfen sind, sondern dass sie in Abhängigkeit von dem verschieden hohen Fettgehalt der jeweiligen Mahlzeit der stillenden Mutter stehen.

Die Fettmenge ist in unseren diesbezüglichen Versuchen gewöhnlich einmal in der Woche bestimmt worden, in das Material wurden dagegen nur die Mittelwerte pro Monat aufgenommen. Die Auswahl der Kost war den Müttern freigestellt.

Das Material des Jahres 1939 ergab einen *Fettgehalt der Muttermilch* von 4,1 % bei Grenzwerten von 1,9 % und 9,6 %. Von YLPÖ ist für die finnische Muttermilch ein Fettgehalt von 4,52 % errechnet worden, woraus hervorgeht, dass der von uns erhaltene Wert ganz bedeutend niedriger ist. GÖLZ hat hingegen, sich auf das Material der Pforzheimer Muttermilchzentrale stützend, für die deutsche Muttermilch einen Fettgehalt von nur 3,5 % erhalten (Grenzwerte 0,5—10,0 %); daraus ist zu ersehen, dass unsere Muttermilch bedeutend fettreicher als die deutsche ist.

In früheren Zeiten ist die Frage, inwieweit die Dauer der Stillperiode auf die Zusammensetzung der Muttermilch Einfluss haben könnte, Gegenstand eifriger Untersuchungen gewesen, wobei man zu dem Ergebnis gekommen ist, dass Zucker- und Fettgehalt während der ganzen Stillzeit im wesentlichen auf derselben Höhe verharren, während hingegen die Eiweiss- und Aschenmenge abnehmen sollen (V. und J. ADRIANCE, CAMERER und SÖLDNER). Auch BIRK hat im Zusammenhang mit seinen an einer 3 Jahre hindurch Milch absondernden Stillenden gemachten Beobachtungen nachgewiesen, dass während der ganzen Dauer dieses langen Prozesses keine wesentlichen Veränderungen eingetreten waren, sondern dass z. B. der Fett-

gehalt prozentuell die ganze Zeit sich auf derselben Höhe gehalten hat. DEGWITZ dagegen führt im Handbuch der Kinderheilkunde von Pfaundler-Schlossmann an, dass bei fortgesetzter Laktation der Gehalt der Muttermilch an Eiweiss, Fett und Zucker geringer wird, im Gegensatz zur Kuhmilch, in welcher eine Zunahme dieser Stoffe wahrzunehmen ist. Aus vorliegender Tabelle (Tabelle 1), in welcher das ganze Material

Tabelle 1.

SALMI			PFEIFFER	V. und J. ADRIANCE
Stillmonat	Anzahl der Fälle	Fettgehalt in %	Fettgehalt in %	Fettgehalt in %
I . . .	14	3,7	2,74	3,71
II . . .	31	4,0	2,04	3,22
III . . .	36	4,1	1,99	3,65
IV . . .	33	4,1	1,77	5,24
V . . .	24	4,1	1,45	3,93
VI . . .	23	3,6	1,54	2,53
VII . . .	20	3,7	1,53	5,81
VIII . . .	19	4,0	1,69	3,73
IX . . .	17	4,4	1,54	4,43
X . . .	14	4,7	1,71	2,93
XI . . .	15	4,6	1,47	3,88
XII . . .	10	4,1	1,73	4,19

nach Stillmonaten verteilt ist, geht Folgendes hervor: *Der Fettgehalt der Muttermilch steigt während der ersten Stillmonate nur wenig, sinkt im 6—8 Stillmonat ganz unverkennbar, um dann in der Folgezeit kräftig anzusteigen.* Auch die amerikanischen Forscher NIMS, MACY, HUNSCHER und BROWN haben nachgewiesen, dass der Fettgehalt der Muttermilch wohl während Anfangsmonate der Stillperiode abnimmt, später aber zu hohen Werten ansteigt. In dieselbe Tabelle sind zu Vergleichszwecken auch die Untersuchungsergebnisse von PFEIFFER und V. und J. ADRIANCE aufgenommen; die Resultate der beiden letzteren erinnern stark an unsere eigenen, während PFEIFFERS



Ergebnisse den unseren bis zu einem gewissen Grade sogar entgegengesetzt sind, m. a. W.: der Fettgehalt soll während der späteren Stillmonate geringer als während der Anfangsmonate sein. Götz hingegen hat an Hand des Materials der Pforzheimer Muttermilchzentrale festgestellt, dass der Gehalt an Fett in der Muttermilch zwei Monate lang ansteigt und dann weiterhin konstant bleibt.

Tabelle 2.

Stillmonat	Fall K. L. %	Fall R. L. %	Fall A. T. %	Fall L. P. %	Fall I. J. %
I . . .	.	3,9	.	.	.
II . . .	.	3,7	3,8	5,2	.
III . . .	3,6	3,7	3,2	5,8	3,1
IV . . .	4,4	3,9	3,4	5,4	3,1
V . . .	4,5	4,1	3,9	5,4	3,1
VI . . .	4,2	4,2	3,8	4,5	3,1
VII . . .	4,3	3,9	3,3	5,1	4,8
VIII . . .	3,2	5,1	2,9	5,3	4,7
IX . . .	11,0	5,4	.	.	3,7
X . . .	.	10,6	.	.	4,1
XI . . .	.	.	.	.	3,9
XII . . .	.	.	.	.	3,9

In Tabelle 2 sind einige Einzelfälle zusammengestellt, bei denen sich die Gelegenheit geboten hatte, den Schwankungen des Fettgehaltes der jeweiligen Muttermilch in den einzelnen Stillmonaten fortlaufend zu folgen. In diesen Fällen treten jedoch die Veränderungen im Fettgehalt der Milch nicht so eindeutig in derselben Richtungweisend wie bei den vorhergegangenen Massenuntersuchungen zu Tage, obgleich auch hier gewisse Hinweise auf Zu- und Abnahme des Fettgehaltes in derselben Richtung wohl zu bemerken sind. So ist z. B. im Fall K. L. ein deutliches Ansteigen des Fettgehaltes vom vierten Stillmonat an und ein Absinken desselben erst im achten Monat festzustellen; Fall R. L. zeigt dieselbe Tendenz, doch

beginnt die Herabsetzung hier schon im siebenten Monat; wenn im Fall A. T. die Schwankungen auch nicht so auffallend sind, so ist die Tendenz doch im allgemeinen dieselbe; im Fall L. P., der einen verhältnismässig hohen Fettgehalt zeigt, ist im sechsten Stillmonat eine deutliche Abnahme desselben zu erkennen; im Fall I. J. hält sich der Fettgehalt in den Anfangsmonaten auf vollständig gleicher Höhe bis dann im siebenten Monat doch ein deutliches Ansteigen festzustellen ist und das Absinken bis in den neunten Monat verzögert ist. — *Es scheint also ganz offensichtlich zu sein, als hätte die Kurve des Fettgehaltes der Muttermilch ihren für die ganze Stillperiode vorgezeichneten Verlauf: sie steigt in den Anfangsmonaten der Stillperiode, fällt im 6—9 Monat, wonach wieder ein neuer Aufstieg beginnt.* Für diese Erscheinung eine hinreichende Erklärung zu finden ist schwer. Vielleicht steht sie im Zusammenhang mit der von PFAUNDLER, DE RUDDER und auch der von YLINEN konstatierten Tatsache, dass der Gipfel der Laktationskurve auf den 5—9 Stillmonat fällt, nach welchem Zeitabschnitt die Milchmenge wieder abzunehmen beginnt. Unter diesen Voraussetzungen würde die ganze abgesonderte Fettmenge doch unverändert bleiben, auch wenn sie prozentuell geringer zu werden scheint.

Im bearbeiteten Material gibt es zahlreiche Fälle, wo die Mütter die Funktion der Brustdrüse sogar nach dem 10.ten Stillmonat noch aufrecht erhalten haben. Für solche Milch wird, mit HOLT, COURTNEY und FALES, die Bezeichnung »Spätmilch« angewandt. Eine Zeitlang herrschte die Auffassung, dass diese Milch von schlechterer Qualität sei als die in der normalen Stillperiode abgesonderte (»reife Milch«). BIRK wies jedoch nach, dass dieses auf einem Irrtum beruhe, da seine, an der schon früher erwähnten, 3 Jahre lang Stillenden gemachten Beobachtungen zeigten, dass ihre Milch qualitativ vollständig auf der Höhe der normalen Milch stand. In Prozenten ausgedrückt hat die »Spätmilch« unseres Materials einen Fettgehalt von durchschnittlich 4,2 %; daraus ist zu ersehen, dass die Fettmenge der »Spätmilch« den für das ganze Material geltenden mittleren Fettgehalt von 4,1 % sogar um 0,1 %

übersteigt. Die »Spätmilch« ist also, was den Fettgehalt anbetrifft, als vollständig gleichwertig mit normaler Milch anzusehen.

Tabelle 3.

Alter der Mutter	Anzahl der Fälle	Fett in %
→ 25 Jahre	7	3,8
25—35 »	49	4,0
älter als 35 Jahre	12	4,4

Qualität und Menge der Milch verändern sich bei ein und demselben Individuum *ceteris paribus* mit zunehmendem Alter. Der höchste Kalorienwert der Menschenmilch ist zwischen dem 15.ten und 20.ten Lebensjahr zu konstatieren, (13 % Trockensubstanz), der niedrigste dagegen zwischen dem 35.ten und 40.ten (10 % Trockensubstanz) (DEGKWITZ). Zwecks Klärung der Frage, ob diese Verschiedenheit der Kalorienwerte der Muttermilch in den einzelnen Altersklassen in Abhängigkeit von der Verschiedenheit ihres Fettgehaltes stehen mag, ist jetzt unser Material nach dem Alter der Mütter in drei Gruppen folgendermassen verteilt worden: 1. Gruppe bis zum 25.sten Lebensjahr, 2. Gruppe 25—35-Jährige, 3. Gruppe ältere als 35 Jahre. Aus Tabelle 3 ersehen wir, dass mit zunehmendem Alter der Mutter der Fettgehalt ihrer Milch ansteigt. Dagegen haben GÖLZ wie auch PEOLA festgestellt, dass das Alter der Mutter keine Bedeutung für die Höhe des Fettgehaltes der Milch hat.<sup>1</sup> Die zwischen den einzelnen Altersklassen unseres Materials herrschenden Unterschiede des Fettgehaltes sind ja wohl relativ unbedeutend und könnten, wenn wir die geringe Anzahl der Fälle in Betracht ziehen, als vom Zufall herrührend angesehen werden; meiner Meinung nach zeigen sie jedoch so viel, dass die in der oben angeführten Angabe von DEGKWITZ behauptete Verschiedenheit der Kalorienwerte der Milch der einzelnen Jahresklassen keinesfalls durch einen verschieden hohen Fettgehalt ihrer Milch bedingt sein kann.

<sup>1</sup> CÉARD hat die Milch einer 65-jährigen algerischen stillenden Grossmutter in ihrer Zusammensetzung als vollständig normal festgestellt.

MACY sowie NIMS, MACY, HUNSCHER und BROWN haben festgestellt, dass bei jeder Mutter die spezifischen Eigenheiten ihrer Milch sowohl in den verschiedenen Stadien derselben Stillperiode wie auch in mehreren auf einander folgenden Stillperioden zu beobachten sind. Dementsprechend wäre zu erwarten, dass die für jede Mutter typische Höhe des Fettgehaltes ihrer Milch sich von einer Stillperiode zu andern wiederholen würde. Daher habe ich zuerst versucht auf Grund meines Materials die Frage zu klären, ob ein wesentlicher Unterschied im Fettgehalt der Milch der in verschiedenen Stillperioden sich befindenden Mütter zu bemerken wäre. I-Paras gibt es in meinem Material 31, II-Paras 28, III-Paras 5 und IV-, V- und VI-Paras nur ganz vereinzelt. Bei den I-Paras erhielt ich durchschnittlich einen Fettgehalt von 3,9 %; bei den II-Paras 4,0 % und bei den III-Paras 3,7 %. Die Anzahl der Multi-Paras ist zu gering, als dass sich aus ihrem Verhalten bindende Schlüsse würden ziehen lassen. Aus den angeführten Zahlen geht hervor, dass jedenfalls *ein wesentlicher Unterschied im Fettgehalt der Milch der einzelnen Laktationsperioden nicht existiert*. Zum Zweck einer präziseren und bindenderen Klarstellung dieser Frage wäre es wichtig, ein und dieselbe Mutter in ihren verschiedenen Laktationsperioden beobachten zu können. Diese Gelegenheit hat sich mir auch in vier Individualfällen geboten: Im Fall K. L., wo es eine V-Para im Jahre 1939 mit einem durchschnittlichen Fettgehalt der Milch von 5 % galt, fanden wir im Jahre 1943 in der 6.ten Laktationsperiode einen Fettgehalt der Milch von nur 3,1 %. Im Fall E. A. handelte es sich im Jahre 1939 um eine III-Para mit einem Fettgehalt der Milch von 4,2 %. Dieser sank im Jahre 1941 in der 4.ten Stillperiode auf nur 3,2 %. Fall O. V. war eine I-Para vom Jahre 1939; der Fettgehalt ihrer Milch betrug damals 3,8 % und im Jahre 1941, in der 2.ten Laktationsperiode, nur 3,2 %; schliesslich haben wir Fall M. G., im Jahre 1939 eine II-Para mit einem Fettgehalt der Milch von 4,3 %; dieser war im Jahre 1941, in der 3.ten Stillperiode, nur noch 2,6 %. Aus allen diesen Individualfällen ist zu ersehen, dass in jeder folgenden Laktationsperiode der Fettgehalt der

Milch gegenüber dem der vorausgegangenen deutlich herabgesetzt ist. Bei Bewertung dieser Tatsache ist jedoch in Betracht zu ziehen, dass die späteren Stillperioden in die Kriegsjahre fielen, wo also die Ernährungslage unseres Landes mit der daraus folgenden strengen Normierung der Nahrungsmittel und den knappen Rationen wohl schon ihren Einfluss hat geltend machen können. Auf diese Seite der Frage komme ich jedoch im weiteren Verlauf meiner Abhandlung, bei Besprechung des Einflusses der kriegszeitlichen Ernährungslage auf die Zusammensetzung der Muttermilch, noch näher zurück.

Die gegenseitige Abhängigkeit der Milchmenge und ihres Fettgehaltes hat das Interesse der Forscher von jeher in hohem Grade gefesselt. Nach AURNHAMMER kommt der Brustdrüse das Vermögen zu, Fett in solch einem Umfange abzusondern, dass die Tages-Fettmenge der Milch konstant bleibt. Nach ENGEL, ZANETTI, LUCIGNANI und auch YLPRÖ stehen sezernierte Milchmenge und Fettgehalt im umgekehrten Verhältnis zu einander. Ein entgegengesetzter Standpunkt wurde dagegen aus dem Kreise früherer Forscher von u. a. HELBICH vertreten, welcher feststellte, dass der Fettgehalt der einzelnen Tagesportionen der Milch sich nicht umgekehrt proportional zu der abgesonderten Milchmenge verhalte; ebenso wies BAMBERG, der seine Versuche über einen recht langen Zeitabschnitt ausdehnte, nach, dass die Zusammensetzung der Milch konstant bleibe, wenn auch das Sezernierungsvermögen der Brustdrüse auf eine beliebige Höhe heraufgepresst wird. RUŽIČIĆ, VINCENT und VIAL sowie WIDDOVS und LOWENFELD sind der Ansicht, dass es überhaupt keine Abhängigkeit zwischen sezernierter Milchmenge und ihrem Fettgehalt gebe. GÖLZ hat auf Grund des Materials der oben erwähnten Pforzheimer Muttermilchzentrale direkt nachweisen können, dass im Gegenteil bei Hypergalaktie die Milch sogar sich als fettreicher erwies als bei Hypogalaktie.

In Tabelle 4 sind speziell die Fälle aufgenommen, deren Fettgehalt der Milch höher als der Mittelwert, d. h. höher als 4,1 % war; gleichzeitig ist ihr %-Gehalt an Fett in Relation gesetzt zu der von ihnen an die Muttermilchzentrale täg-

Tabelle 4.

Fall	Fettgehalt in %	Täglich gelieferte Milchmenge L.	Fall	Fettgehalt in %	Täglich gelieferte Milchmenge L.
K. L. . .	5,0	1,5	A. M. . .	5,0	1,0
G. L. . .	4,8	0,2	S. P. . .	4,4	0,9
H. L. . .	4,8	1,0	R. P. . .	4,8	0,6
R. L. . .	5,8	1,8	L. P. . .	5,2	0,4
S. K. . .	5,1	0,4	H. R. . .	5,2	1,5
E. A. . .	4,2	1,8	M. K. . .	4,5	0,4
S. R. . .	7,2	1,0	S. M. . .	4,8	0,8
A. K. . .	5,1	0,8	E. A. . .	4,6	0,8
M. S. . .	4,6	0,8	M. V. . .	5,2	0,2
A. S. . .	5,1	0,6	K. J. . .	9,6	2,0
M. T. . .	4,9	0,4	E. V. . .	4,4	0,8
H. Ä. . .	5,2	1,0	A. K. . .	5,7	0,5
J. L. . .	5,8	0,5	M. G. . .	4,8	1,8
E. L. . .	4,4	0,5			

lich gelieferten Milchmenge. Wenn diese letztere auch nicht der tatsächlich von der Mutter produzierten Milchmenge entspricht, so ist sie doch relativ verwertbar und gibt ein genügend klares Bild von der Sekretionsfähigkeit jeder Mutter. Im allgemeinen müssen wohl alle Mütter der Muttermilchzentrale schon deswegen als milchreich angesehen werden, weil sie ja nur die über ihren eigenen Bedarf hinausgehende Milch zur Zentrale bringen. Aus Tabelle 4 ersieht man, dass fettreiche Milch sezernierende Mütter in den meisten Fällen auch zu den Milchreichen gehören, worunter ich solche Fälle verstehe, deren an die Muttermilchzentrale täglich gelieferte Milchmenge wenigstens 0,5 Liter beträgt. Solcher Fälle gibt es 17 von den hier angeführten 27 (63 %). — Andererseits finden sich unter den mässig fettreichen und fettarmen Milch absondernden Müttern unseres Materials (im ganzen 41 Fälle) 15 besonders milchreiche von 41 (36,5 %), also erheblich weniger als in der vorigen Gruppe. Betrachtet man die besonders

fettarme Milch (unter 3 %) sezernierender Mütter noch für sich, so sieht man, dass es unter ihnen überhaupt keine wirklichen »Grossstillenden« gibt. Wir können also als eine von uns festgestellte Tatsache aussprechen, dass ein hoher Fettgehalt der Muttermilch durchaus nicht im umgekehrten Verhältnis zur produzierten Milchmenge steht, sondern ist im Gegenteil die Sachlage eher eine solche, dass *eine an Milch reiche Mutter meist auch fettreiche Milch absondert*.

Besondere Erwähnung und Beachtung verdient Fall K. J. Hier hatte eine 41-jährige IV-para der Muttermilchzentrale im Laufe von 2 1/2 Jahren 1514 Liter Milch geliefert, deren Fettgehalt im Durchschnitt 9,4 % und deren Grenzwert 12,2 % betrug. Dieses dürfte wohl ein in der Literatur einzig dastehender Fall sein. Das Befinden der Mutter während der ganzen Stillzeit war gut, das Gewicht stieg sogar von 57 1/2 auf 75 kg. Die Milchsekretion hätte wohl noch weiter fortgesetzt, doch verhinderte Wegzug aus der Stadt ein weiteres Fortsetzen der Milchliefierungen.

Es ist in der Viehwirtschaft eine bekannte Tatsache, dass der Fettgehalt der Milch in den Frühjahrsmonaten, wo die Ernährung des Viehs ehe es auf die Weide kommt sowohl knapp wie einseitig ist, stark sinken kann. In der medizinischen Literatur bin ich nicht einmal auf eine Erwähnung von Saisonschwankungen des Fettgehaltes der Muttermilch gestossen. Da nun aber nach den Untersuchungen des Volksernährungskomitees in der Nahrung der weniger bemittelten Volksschichten unseres Landes beachtenswerte Unterschiede zwischen deren Frühjahrs- und Herbstkost in der Richtung bestehen sollen, dass die Nahrung in den Frühlingsmonaten in jeder Hinsicht, sowohl was Kalorien als Vitamine betrifft, knapper ist (VIRTANEN und TURPEINEN), so besteht die Möglichkeit, dass auch dieser Umstand einen Einfluss auf den Fettgehalt der Muttermilch haben könnte. Zur Beleuchtung dieser Frage ist auf Grund unseres Materials v. J. 1939 der durchschnittliche Fettgehalt der Milch für die einzelnen Monate in % berechnet worden und in folgender Tabelle (Tab. 5) angeführt.

Aus dieser Tabelle geht hervor, dass wir als *mittleren Fettgehalt der Milch für die erste Jahreshälfte (Januar—Juni) 3,9 %* und *für die zweite Jahreshälfte (Juli—Dezember) 4,5 % erhalten*, worin doch ein deutlicher Unterschied zu ersehen ist. Das Ansteigen des Fettgehaltes setzt augenscheinlich im Juli ein. Ebenso hat SINKKO nachgewiesen, dass der C-Vitamingehalt unserer Muttermilch Schwankungen in derselben Richtung unterworfen ist; er fand ihn am niedrigsten im Januar—Februar und am höchsten im Juli—September.

Tabelle 5.

	Jan.	Febr.	März	April	Mai	Juni
Fett-%	4,0	3,8	3,8	3,9	4,1	3,9
	3,9 %					
	Juli	Aug.	Sept.	Okt.	Nov.	Dez.
Fett-%	4,5	4,6	4,5	6,0	4,5	3,4
	4,5 %					

In mehreren Individualfällen habe ich den Schwankungen des Fettgehaltes der Muttermilch in den einzelnen Kalendermonaten folgen können und dabei bemerkt, dass in einigen Fällen der Fettgehalt tatsächlich während der Monate des 2.ten Halbjahres grösser zu sein scheint als im 1.ten Halbjahr. So beginnt im Fall R. L. ein Anstieg ganz entschieden erst im August, während er im Fall I. J. schon so früh wie im Mai eintritt. In andern Fällen dagegen ist diese Anstieg-tendenz nicht zu bemerken gewesen.

Obenerwähnte Untersuchung des Volksernährungskomitees betrifft zu  $\frac{4}{5}$  die Landbevölkerung, deren Kost naturgemäss wesentlich einseitiger wie auch knapper als die der Stadtbevölkerung ist. Zu unserem Material hingegen gehören ausschliesslich Städterinnen, denen mehr Möglichkeiten für eine abwechslungsreichere Kost zu Gebote stehen. Ungeachtet dessen bemerkten auch wir einen deutlichen Unterschied zwischen dem Fettgehalt der Muttermilch der Frühlings- und dem der Herbstmonate. Daraus könnte man den Schluss ziehen, dass



auch in der Stadt die weniger bemittelten Mütter im Frühjahr auf knapperer Kost gelebt haben als im Herbst. Auf diese Frage werde ich im Weiteren bei Besprechung des Einflusses der Kriegsernährung auf die Zusammensetzung der Muttermilch und speziell ihren Fettgehalt noch näher zurückkommen.

## II.

Nachfolgende, die Muttermilch betreffende, Untersuchungen wurden z. T. in den Kriegsjahren 1941—42, z. T. auch 1943 angestellt. Bestimmungen des Fettgehaltes der Muttermilch wurden an der Milch von 130 Müttern vorgenommen. Dabei konnte jetzt nur 3,1 % als *mittlerer Fettgehalt* der Muttermilch mit 1,1 % und 6,5 % als Grenzwerte festgestellt werden, woraus hervorgeht, dass der Fettgehalt der Muttermilch in den Jahren 1941—42 um ca. 25 % gegen das Jahr 1939 gesunken war. Hierbei ist speziell zu beachten, dass fettreiche Milch absondernde Mütter in äusserst geringer Anzahl vorkamen, denn mehr als 5 % Fett enthaltende Milch trafen wir nur in 4,6 % (14,7 % im Jahre 1939) aller Fälle des Gesamtmaterials. Schon oben ist auf einige Individualfälle hingewiesen worden, bei denen es im Jahre 1939 möglich gewesen war, Fettgehaltbestimmungen der Milch vorzunehmen; bei denselben Müttern wurden während erneuter Stillperioden 1941 und 1943 dieselben Bestimmungen ausgeführt und war bei ihnen allen eine deutliche Herabsetzung des Fettgehaltes in den Kriegsjahren zu beobachten.

Es bot sich im Jahre 1943 die Gelegenheit, bei 14 Müttern ausser den Fettbestimmungen auch Analysen der Muttermilch bezüglich Eiweiss, Milchzucker und Asche zu machen (Tab. 6). Zu Vergleichszwecken sind im Folgenden YLPPÖS im Jahre 1928 veröffentlichten, finnische (5 Ammen und 1 Mutter) sowie auch deutsche Muttermilch betreffende, Analysenwerte mitangeführt.

Aus Obigem erhellt, dass bei uns die Muttermilch der jetzigen Kriegszeit ausser im Zuckergehalt, auch in jeder andern Hinsicht die Werte der Friedenszeit in bedeutendem Grade

Tabelle 6.

	SALMI %	YLPPÖ %	Milch der deutschen Mutter %
Fett . . . . .	3,48	4,52	3,31
Eiweiss . . . . .	0,85	1,20	0,95
Milchzucker . . .	6,22	6,48	6,81
Asche . . . . .	0,18	0,20	0,19

untersteigt. So ist der *Fettgehalt* um 22,71 %, der *Eiweissgehalt* um 27,5 % und die *Aschenmenge* um 35 % gesunken. Der am wenigsten einer Veränderung unterworfenen Bestandteil der Milch scheint der Zucker zu sein, indem sein Gehaltswert nur um 4 % gegen den seinerzeit von YLPPÖ bestimmten herabgesetzt ist. Unter diesen Voraussetzungen müsste auch der Kalorienwert der *Kriegszeit-Muttermilch* erheblich geringer geworden sein als der der *Friedenszeit*. In der Tat erhielten wir auch nur 606 Kal. als *Kalorienwert der Milch für das Jahr 1943*, während im Jahre 1928 YLPPÖ 726 Kalorien festgestellt hatte und der Kalorienwert der deutschen Muttermilch damals 619 betrug. Demzufolge ist unsere *Kriegszeit-Muttermilch* in bezug auf ihren Kalorienwert ungefähr von gleicher Beschaffenheit wie die deutsche Muttermilch der *Friedenszeit*. Bei seinen während des vorigen Weltkrieges vorgenommenen Untersuchungen hatte LEDERER den damaligen Kalorienwert als 500—600 bestimmt.

Aus obigen Feststellungen geht also hervor, dass in der *Zusammensetzung der Muttermilch* während der *Kriegszeit* eine grosse Verschiebung in der Hinsicht stattgefunden hat, dass der *Eiweiss- und Fettgehalt* sowie die *Aschenmenge* abgenommen haben. Es taucht sofort die Frage auf, wodurch dieser Umstand bedingt ist. Ist er eine Folge der durch die *Kriegszeit* erschwerten Ernährungslage? Als während des vorigen Weltkrieges breite Volksschichten Deutschlands und mit ihnen, ungeachtet ihrer vielen Extrarationen, auch die stillenden

Mütter gezwungen waren, mit äusserst knapper Kost ihr Leben zu fristen, erwachte das Interesse für die eventuell qualitativ in der Muttermilch stattgehabten Veränderungen. Einige Forscher (KAUPE, RUGE, HOTZEN, BERGMANN) versuchten aus Untersuchungen über Befinden und Entwicklung der Kriegszeit-Brustkinder auf die Qualität der Muttermilch zu schliessen. Dieses indirekte Untersuchungsverfahren ist aber unsicher und fordert, wenn auf seiner Basis irgendwelche bindenden Schlüsse gezogen werden sollen, ein besonders umfangreiches Material, das aber den genannten Forschern nicht zur Verfügung stand. Bei Anwendung des direkten Untersuchungsverfahrens jedoch haben MOMM und KRÄMER keinen Unterschied in der Zusammensetzung der Muttermilch im Vergleich zur Muttermilch der Friedenszeit bemerken können. Bald darauf hat PASCH festgestellt, dass auch die Nachkriegskost den Fettgehalt der Muttermilch nicht sichtbar beeinflusst hat. KLOTZ dagegen beobachtete in der Kriegszeit-Brustmilch einen besonders grossen Fett- und Eiweissmangel; LEDERER konstatierte auch eine Abnahme dess Fett- aber gleichzeitig auch des Zuckergehaltes.

Nun gibt es andererseits auch Versuche, während welcher man durch Veränderung der Zusammensetzung der Kost der Mütter auf die Zusammensetzung der Milch einzuwirken bestrebt gewesen ist. Aus der Viehwirtschaft ist es nämlich bekannt, dass durch Anwendung gewisser Fütterungsverfahren sowohl Menge wie Qualität der Milch in gewünschter Richtung beeinflusst werden können. Bei Übertragung derselben Massnahmen auf Menschenmaterial haben die Ergebnisse dieser Experimente sich jedoch als mehr oder weniger unsicher erwiesen. Aus dem Moskauer Armenhause (ZUKOWSKY) sind schon im Jahre 1871 gemachte Beobachtungen veröffentlicht worden, laut welchen die äusserste Fettarmut der Kost in der Fastenzeit eine, wenn auch nur vorübergehende, Abnahme des Fettgehaltes der Muttermilch zur Folge hatte. ROCHLINA und LUKJANOWITSCH haben auch festgestellt, dass Fettmangel der Kost wohl einen Einfluss auf den Fettgehalt der Milch ausübe, dass aber im übrigen zwischen der Milchlungernder und reichlich ernährter Mütter kein eigentlicher Unterschied bestehe.

Andererseits teilt JOHANNESSEN mit, dass es ihm gelungen sei, bei unterernährten Müttern den Fettgehalt ihrer Milch durch Fettzugabe zu ihrer Kost zum steigen zu bringen. Ebenso stellte auch ERSTEIN fest, dass es durchaus im Bereich der Möglichkeit liegt, bei Müttern, deren Milch fettarm ist, durch Zugabe zu ihrer Kost von reichlich Fett in Form von Butter, Schweinefleisch oder Milch, den Fettgehalt ihrer Milch zu heben. Zum selben Ergebnis sind auch MALAGODI, FINIZIO und MOLL gekommen. PASCH konnte dagegen feststellen, dass bei Stillenden, welche eine reichliche Kost und 1,5 Lit. Milch täglich erhielten, der Fettgehalt der Milch nur 3,54 % betrug, während hingegen die Milch der unbemittelten Mütter der Beratungsstationen, die auf knapper Kost lebten, einen Fettgehalt von 4,5 % aufwies. FERRAROS Untersuchungen wiederum haben gezeigt, dass, wenn zur gewohnten Kost der Stillenden Fett, Eiweiss oder Kohlehydrate zugesetzt werden, keinerlei Einfluss auf Menge und Zusammensetzung der Milch zu bemerken ist. Besonders auffallend sind aber die Untersuchungen RUŽIĆ, aus welchen hervorgeht, dass der Fettgehalt der Muttermilch in Abhängigkeit vom Fettgehalt der Kost der Mutter stehe und im engen Zusammenhang mit diesem in der Weise variere, dass schon 3 Stunden nach einer Fettmahlzeit der Fettgehalt der Milch zu steigen beginnt, nach 12 Stunden den Höhepunkt erreicht hat und im Laufe der nächsten 12 Stunden wieder abnimmt. Ebenso haben die Amerikaner SHUKERS, MACY, NIMS, DONELSSON und HUNSCHER festgestellt, dass der Fettgehalt der Muttermilch in Abhängigkeit vom Fettgehalt der aufgenommenen Nahrung stehe.

Aus den eben angeführten vielen sich z. T. widersprechenden Literaturangaben geht jedenfalls eines hervor, nämlich dass, wenn auch die Untersuchungen zu sehr verschiedenen Resultaten geführt haben, die Zusammensetzung der Kost der Stillenden doch bis zu einem gewissen Grade ihre Bedeutung für die Zusammensetzung der Muttermilch hat. Natürlich ist jeder einzelnen Mutter eine individuelle typische Zusammensetzung ihrer Milch eigen, die unter besonderen Verhältnissen

bis zu einem gewissen Grade variieren kann. Es gibt z. B. Mütter, die unter normalen Verhältnissen fettreiche und andere, welche fettarme Milch absondern. Tritt dann eine Abweichung in der gewohnten Kost oder in dem Verhältnis ihrer einzelnen Bestandteile zu einander ein, so kann dieses eine Veränderung in der Zusammensetzung der Milch zu Folge haben. Ich habe u. a. feststellen können, dass die Zusammensetzung der Muttermilch jetzt in den Kriegsjahren sich in der Weise verändert hat, dass ihr Fett- und Eiweissgehalt wie auch ihre Aschenmenge in hohem Grade abgenommen haben, was natürlich auch ein Sinken ihres Kalorienwertes zur Folge gehabt hat. Daher liegt der Gedanke sehr nahe, dass unsere knappe Kriegszeit-Ernährung beim Zustandekommen dieser Veränderung mitbeteiligt gewesen ist. Zwecks Klärstellung dieser Frage muss man sich vor allem die Umwälzungen in der Ernährungslage, welche die im Zusammenhang mit dem Kriege eingeführte Reglementierung der Lebensmittel nach sich gezogen hat, vor Augen halten. Im Jahre 1941 war man wegen ungünstiger Witterungsverhältnisse und begrenzter Einfuhrmöglichkeiten gezwungen, die Lebensmittelrationen bedeutend einzuschränken. Ganz besonders betraf diese Massnahme die Fettrationen. So erhielt z. B. im Dezember ein Normalverbraucher nur 150 Gr. Nahrungsfett. In den Wintermonaten des Jahres 1942 konnten die Fettrationen ein wenig vergrössert werden, doch kam ein Normalkonsument auch jetzt nicht über 300—400 Gr. pro Monat hinaus. Gleichzeitig wurden aber auch die Brot- und Fleischrationen bedeutend herabgesetzt, wozu in Helsinki jedenfalls noch ein ernster Mangel an Kartoffeln und Gemüse hinzukam. Als Folge davon war denn auch das Defizit an Eiweisstoffen in der Kost ausserordentlich stark; denn ausser den minimalen Fleischrationen stand auch Fisch nur in kaum nennenswerter Menge zu Gebote. Als Zulage zu diesen Grundrationen erhielten stillende Mütter 500 Gr. Butter im Monat, 4 dl. Milch am Tage und 1 Kg. Eier oder alternativ 750 Gr. Käse oder eine gewisse Menge Fleisch im Monat. Daraus ersieht man, dass unsere offizielle Ernährungslage im Grunde genommen

recht prekär war; allerdings verbesserte sich im Jahre 1943 die Lage ein wenig durch eine Reihe Extra-Austeilungen von Nahrungsfett. Es ist berechnet worden, dass der Normalverbraucher in Form von Mehl, Fett, Fleisch und Zucker ungefähr 1350 Kal. am Tage erhielt. Dazu kamen eine geringe Menge anderer reglementierter und eine Anzahl ausserhalb der Reglementierung stehender Lebensmittel, so dass der gesamte Kalorienwert der Kost ca. 2000 Kal. betrug. Fügt man hierzu den durch die Spezialrationen für stillende Mütter bedingten Kalorienzuschuss, ca. 400 Kal., so erhält man als Totalsumme 2400 Kal. SCHICK hat berechnet, dass eine ihre Arbeit im Stehen ausführende Frau pro Tag 2000 Kal. und eine stillende Mutter pro jedes abgesonderte Gramm Milch eine Zulage von 1 Kalorie, d. h. pro 1 Liter Milch 1000 Kalorien braucht. Demzufolge bedarf also eine 1 Liter Milch absondernde Mutter ca. 3000 Kalorien, woraus für unsere damaligen Verhältnisse ein Defizit von ca. 600 Kal., d. h.  $\frac{1}{4}$  der ganzen Menge, zu ersehen ist. Dieses Defizit ist aller Wahrscheinlichkeit nach noch grösser gewesen, da die meisten unserer Frauen aus Arbeiterfamilien stammten, für die sie im Haushalt schwere körperliche Arbeit zu leisten gezwungen waren. Vom Ende des Jahres 1941 an haben die Mütter, die der Muttermilchzentrale täglich wenigstens  $\frac{1}{2}$  Liter Milch liefern, als Extra-Zugabe zu den früher genannten 450 Gr. Nahrungsfett, 450 Gr. Zucker und eine gewisse Menge Getreideprodukte (C-Karte) pro Monat erhalten, was im Ganzen ca. 200—300 Kal. pro Tag ausmacht. Mütter, die täglich wenigstens 1 Liter Muttermilch liefern, erhalten als Zugabe zu den eben erwähnten Extra-Rationen pro Monat noch 250 Gr. Nahrungsfett, 250 Gr. Zucker und etwas Getreideprodukte (D-Karte), d. h. 150—200 Kal. pro Tag. Diese Zusatzrationen sind im Verhältnis zu den gelieferten Milchmengen natürlich äusserst knapp, obgleich sie andererseits doch ihre gute Seite haben, indem sie als Sporn zur Erweckung des Willens zum Stillen bei den Müttern dienen. Fügen wir zum Gesagten noch hinzu, dass in den meisten Fällen die in unser Material gehörenden Mütter unbemittelt und zum Lebensun-

terhalt auf die Reservistenlöhne ihrer Männer angewiesen waren, daher also auch keine Möglichkeit hatten, sich Lebensmittel durch Umgehung der Reglementierung zu verschaffen, so ist man wohl gezwungen zuzugeben, dass ihre Ernährung sehr knapp und einseitig gewesen ist. Andererseits kann man aber auch durchaus nicht von einer regelrechten Hungersnot sprechen, denn die Mütter waren während der Stillzeit durchaus nicht bei schlechtem Allgemeinbefinden und magerten nicht einmal in höherem Masse ab; im Gegenteil zeigten viele von ihnen sogar Gewichtszunahme. Gewiss, es war in dieser Hinsicht insofern ein gewisser Unterschied im Vergleich zum Jahre 1939 zu bemerken, als damals von den Milchspenderinnen der Muttermilchzentrale 39 % Gewichtszunahme zeigten, 51 % abmagerten und 10 % ihr früheres Körpergewicht beibehielten, während unter den Müttern des Kriegsmaterials das Gewicht nur bei 26 % zunahm, bei 54 % sank und bei 20 % unverändert blieb. Es ist daher kaum anzunehmen, dass die Kalorienarmut der Nahrung an sich Ursache zur Verschlechterung der Qualität der Muttermilch sein dürfte. Es mag viele verschiedene Ursachen für diese Erscheinung geben, doch ist unter ihnen jedenfalls der geringe Fett- und Eiweissgehalt unserer Nahrung eine von den wichtigsten.

Es ist auch der Gedanke aufgeworfen worden, ob nicht der Vitamingehalt der Nahrung vielleicht irgend eine Rolle in der Zusammensetzung der Muttermilch spielt, und ob nicht vor allem der Vitamin B-Komplex in dieser Hinsicht einen wichtigen Faktor darstellt. SURE, BOGGS, WALKER und STUART haben in Tierversuchen gezeigt, dass der Bedarf der Säugenden an B-Vitaminen zur Erreichung des Wachstumoptimums der Nachkommenschaft 3 Mal so gross wie der Normalbedarf ist. So hat SURE auch beobachtet, dass durch Zusatz von Hefekonzentrat zur Nahrung des säugenden Muttertieres ein besonders gutes Wachstum der Jungen erzielt wird. DONELSON und MACY konnten in Menschenversuchen durch Hefebeigabe die biologische Wirkung der Muttermilch verstärken wie auch gleichzeitig das subjektive Befinden der Mütter bessern. SHODA erreichte durch Hefe ein Ansteigen des Laktosegehaltes der



Muttermilch. Es ist auch in der Volksmedizin von jeher bekannt, dass die Hefe für schwangere und stillende Frauen besonders als ein für die Vermehrung der Milchproduktion wichtiges Agens von grosser Bedeutung sei. Von da lässt sich auch die Anwendung verschiedener Schwachbiersuppen in der Kost während der Stillzeit herleiten. Auch in der Tierzucht hat man dieser Frage grössere Beachtung geschenkt. In den Kriegsjahren 1914—1918 experimentierte man in grossem Umfang mit der Anwendung von Mineralhefe als Ersatz für Eiweisstoffe bei Fütterung des Viehs, allerdings mit recht mageren Resultaten. Hierbei wurde von einem Teil der Forscher angenommen, dass der hohe Nährwert der Hefe auf ihrem hohen Gehalt an stickstoffhaltigen Stoffen beruhe (BERGIUS, SCHOLLER, FINGERLING u. a.), während SCHÜLEIN dagegen grossen Wert auf ihren Vitamingehalt ( $B_1$ ) legt. LUCADOU stellte fest, dass bei täglicher Verfütterung an Kühe von 5 Gr. gewöhnlicher Backhefe, der Fettgehalt der Milch schon nach 3 Tagen von 4,1 % auf 5,1 %, also um 25 % gestiegen war. Ausserdem beobachtete er, dass die gesonderte Verabreichung von Lactoflavin oder Aneurin keinen Einfluss auf den Fettgehalt der Milch hatte. Wurden dagegen beide Vitamine gleichzeitig im Verhältnis von 20 mg.  $B_1$  und 6 mg.  $B_2$  gereicht, so begann der herabgesetzte Fettgehalt wieder zuzunehmen. Auf die Milchmenge hatten diese Beigaben jedoch keinen Einfluss. GREINER und MOSONYI erreichten in 41 % ihrer Fälle eine Zunahme des Fettgehaltes der Muttermilch durch Zusatz von Ovomaltine zur Kost der Mutter; gleichzeitig stieg auch in 33 % der Fälle die Aschenmenge der Muttermilch um einiges. Einen Einfluss auf die übrigen Bestandteile der Milch haben die beiden Autoren nicht beobachten können. Sie nehmen an, dass die Wirkung des Ovomaltines von dessen grossem Gehalt an A- und B-Faktor herrühre.

Um einen Einblick in die Frage zu gewinnen, ob die Verminderung des Fettgehaltes der kriegszeitlichen Muttermilch eventuell vom  $B_1$ -Vitaminmangel herrühre und ob durch Zugabe von B-Vitamine enthaltenden Stoffen zur Kost der stillenden Mutter es nicht gelingen würde, den Fettgehalt der



Tabelle 7.

Datum 1943	S t i l l e n d e					
	A. A. Fettgehalt in %	A. S. Fettgehalt in %	E. E. Fettgehalt in %	L. M. Fettgehalt in %	T. P. Fettgehalt in %	B. V. Fettgehalt in %
26. XI.	2,8	4,1	2,6	4,1	2,8	1,8
27. »	4,2	3,6	2,7	2,7	3,8	3,8
28. »	2,8	3,2	2,0	3,2	3,8	4,0
29. »	2,9	4,1	3,8	3,6	3,9	2,0
30. XI.	1,4	3,9	2,1	2,9	2,6	4,2
1. XII.	2,0	2,5	2,1	3,8	3,8	2,9
2. »	2,1	3,1	2,1	4,1	3,2	2,9
3. »	1,9	3,0	1,9	3,7	2,8	3,3
4. »	1,5	2,8	1,6	3,7	3,0	3,4
5. »	1,9	2,6	2,0	3,6	3,6	2,2
6. »	2,1	2,8	2,1	2,9	2,9	3,1
7. XII.	2,4	3,0	3,8	2,8	3,5	4,1
8. »	2,8	3,6	3,0	2,6	2,8	3,2
9. »	2,9	3,5	3,1	2,9	3,6	3,1

Muttermilch zu heben, stellte ich eine 2 Wochen dauernde Versuchsserie an 6 Stillenden der »Burg der Kinder« an, von denen eine jede täglich 20 Gr. gewöhnliche Hefe erhielt, wobei die Kost im übrigen unverändert blieb und scharf überwacht wurde. Der Fettgehalt der Milch wurde in der Weise bestimmt, dass von den Stillenden, die kein eigenes Kind mehr stillten, die Proben der ganzen Tagesmischmilch entnommen wurden, während von solchen Stillenden, deren Kinder noch die Mutterbrust erhielten, die Probe aus dem Gemisch des Anfangs- und End-Abmelkens während einer bestimmten Mahlzeit (10 Uhr) genommen wurde. An den ersten vier Tagen der Versuchsserie erhielten die Stillenden ihre gewöhnliche Kost ohne Hefe, an 7 darauf folgenden Tagen als Zusatz zu ihrer Kost die Hefegabe und an den 3 letzten Tagen wurde

dieser Zusatz wieder weggelassen. Aus Tabelle 7 ersehen wir, dass durch die Hefegabe jedenfalls kein Anstieg des Fettgehaltes erzielt wurde, sondern dass der Tages-Fettgehalt, in % ausgedrückt, während der ganzen Versuchszeit sich auf derselben Höhe hielt. Aus all diesen Beobachtungen kann geschlossen werden, dass der geringe Fettgehalt der kriegszeitlichen Muttermilch jedenfalls nicht vom B-Vitaminmangel unserer Kost herrührt und infolgedessen auch nicht durch Zusatz von B-Vitaminen zur Nahrung gehoben werden kann; in keinem Fall ist dieses beim Menschen in Form von Hefefütterung zu erreichen, wie es LUCADOU in seinen Tierversuchen gelungen war.

Tabelle 8.

Mutter	Frühling 1941 Fettgehalt in %	Herbst 1941 Fettgehalt in %
I. J. . . . .	3,3	5,1
A. K. . . . .	1,9	3,6
S. L. . . . .	1,9	3,2
M. M. . . . .	2,9	3,3
K. V. . . . .	2,5	3,2
A. V. . . . .	3,9	2,6
I. V. . . . .	3,4	4,3
A. H. . . . .	3,2	2,3

In Zusammenhang mit der Besprechung des Materials vom Jahre 1939 wurde erwähnt, dass hinsichtlich des Fettgehaltes der Muttermilch gewisse Saisonschwankungen zu bemerken seien und zwar, dass die Milch der ersten Jahreshälfte fettärmer sei als die der zweiten. Dieselbe Erscheinung wiederholt sich auch beim Material der Kriegszeit. So wurde im Frühling 1941 als mittlerer Fettgehalt der Muttermilch 2,7 % (62 Mütter), im Herbst dagegen 3,4 % (46 Mütter) festgestellt. Wie Tabelle 8 zeigt, beobachtet man mit einigen Ausnahmen auch an den einzelnen Müttern, dasselbe Phänomen. Diese Feststellung bestärkt meine Ansicht, dass unter unseren Ver-

hältnissen und bei unserer Kost im Fettgehalt der Muttermilch von der Jahreszeit abhängige Saisonschwankungen auftreten können, indem sich die Muttermilch in den Frühlingsmonaten als bedeutend fettärmer erweist als in den Herbstmonaten.

### **Zusammenfassung.**

Der Fettgehalt der von 68 Milchspenderinnen an die Muttermilchzentrale im Jahre 1939 gelieferten Milch ist nach Gerbers Verfahren bestimmt worden, wobei ein mittlerer Fettgehalt von 4,1 % (Grenzwerte 1,9 %—9,6 %) erhalten wurde. Die fettreichste Milch wurde bei den Mahlzeiten um 10 oder 14 Uhr festgestellt, die fettärmste dagegen früh am Morgen oder spät am Abend.

In den Anfangsmonaten der jeweiligen Stillperiode steigt der Fettgehalt nur wenig, fällt dann während des 6—9 Monats, wonach ein neuer Anstieg beginnt.

»Spätmilch« (= Milch nach dem 10. Stillmonat) ist hinsichtlich des Fettgehaltes gleichwertig mit Normalmilch.

Bezüglich des Fettgehaltes der Milch unterscheiden sich die einzelnen Stillperioden nicht wesentlich von einander.

Eine milchreiche Mutter sezerniert auch meist fettreiche Milch.

Milch der Frühjahrsmonate ist fettärmer als die der Herbstmonate.

In den Kriegsjahren 1941—1943 an 130 Milchspenderinnen angestellte Untersuchungen ergaben, dass der mittlere Fettgehalt der Muttermilch nur 3,1 % betrug, (Grenzwerte 1,1 %—6,5 %), m. a. W. gegen das Jahr 1939 um 25 % gesunken war.

Im Jahre 1943 wurden an 14 Muttermilchproben ausser auf Fettgehalt Analysen auch auf Gehalt an Eiweiss, Zucker und Asche angeordnet; dabei erwies sich der Fettgehalt um 22,71 %, der Eiweissgehalt um 27,5 %, der Zuckergehalt um 4 % und die Aschenmenge um 35 % niedriger als die von YLPPö im Jahre 1928 erhaltenen Werte; gleichzeitig war der Kalorienwert der Milch um 120 Kal. gesunken (606 Kal. pro

726 Kal.). Die Ursache für dieses Wert-Sinken der kriegszeitlichen Milch ist sichtlicherweise in dem knappen Fett- und Eiweißgehalt unserer kriegszeitlichen Kost zu suchen.

Eine tägliche Zugabe von 20 Gr. Backhefe zur Kost der Mütter hatte keinerlei Einfluss auf den Fettgehalt der Muttermilch.

Auch in den Kriegsjahren konnte beobachtet werden, dass die Milch der Frühlingsmonate fettärmer ist als die der Herbstmonate.

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## **Weitere Studien über Bakterien der Coligruppe bei der akuten Dyspepsie und Intoxikation im Säuglingsalter.**

Von

**Dr. med. R. KYRKI.**

Die Pathogenese der akuten Dyspepsie und Intoxikation des Säuglings ist schon lange der Gegenstand eingehender Untersuchungen gewesen. Als die Bakteriologie sich entwickelte, suchte man eifrig nach einem spezifischen Erreger dieser Krankheit, der sog. Cholera infantum. Da jene Bestrebungen jedoch erfolglos blieben, wurde die Hypothese aufgestellt, dass ein unter normalen Zuständen harmloses Bakterium, beispielsweise der Colibazillus, eine Umwandlung durchmachen und gefährlich, krankheitserregend werden könne. ESCHERICH glaubt nicht an eine derartige Umwandlungsfähigkeit des gewöhnlichen Darmcolibazillus, sondern hält es für wahrscheinlich, dass gewisse, dem gewöhnlichen Colibazillus verwandte Arten existieren, welche Darminfektionen hervorrufen können. Diese Annahme wurde gestützt durch mehrere bei Tieren auftretende Darmerkrankungen, bei denen entweder Colibazillen oder diesen verwandte Bakterien gefunden wurden. Die Auffassung, dass die akute Dyspepsie des Säuglings eine Infektionskrankheit sei, die durch viele verschiedene Bakterien hervorgerufen werden könne, macht sich noch eben unter den angelsächsischen Forschern geltend. Sie haben in den Fäzes von Kranken verschiedene, hauptsächlich der Dysenterie-, Paratyphus- oder Coli-Paracoli-Gruppe angehörende Bazillen festgestellt (JOHNSTON, BROMUS, TISDALL, FRASER, BLOCH u. a.). Die Bedeutung des Paracolibazillus hat in letzter Zeit auch der deutsche Forscher DEAK hervorgehoben. BLOCH hält den Colibazillus in den

meisten Fällen für den Erreger, obschon dies wahrscheinlich nie so bindend bewiesen werden könne, wie z. B. die Rolle des Typhusbazillus beim Typhus. Der hervorragendste Vertreter der französischen Pädiatrik MARFAN ist der Meinung, dass es sich bei der eigentlichen Intoxikation (Diarrhoe choleriforme) um eine durch einen exogenen, bisher unbekannten Erreger hervorgerufene Infektion handle. NYBERG fand in den Fäzes von Intoxikations- und Dyspepsiekranken Paracoli- (MORGAN) und Dysenterie- (FLEXNER) Bazillen, dazu Formen von MASSINIS Coli mutabile. Er hält es für wahrscheinlich, dass auch die gewöhnlichen Colibazillen pathogen werden können, weshalb es schwer sei, die Erreger von Diarrhöen mit Bestimmtheit zu definieren. In der deutschen Kinderheilkunde wurde die Bedeutung der Infektion in der Ätiologie der akuten Dyspepsie und Intoxikation ganz und gar durch CZEERNYS und FINKELSTEINS bekannte Theorien von der Rolle der Nahrung nebst anderen Faktoren bei jenen Krankheitszuständen in den Schatten gestellt. Erst i. J. 1917 richtete sich dort das Interesse von neuem auf die Bedeutung der Darmbakterien, als MORO feststellte, dass bei Kindern, welche einer Intoxikation erliegen waren, die sonst vollkommen bakterienfreien obersten Teile des Dünndarms regelmässig Colibazillen enthielten. BESSAU und BOSSERT, SCHEER u. a. konstatierten mit Hilfe von Magen- und Duodenalsondierungen, dass bei akuter Dyspepsie und Intoxikation, auch in solchen Fällen, wo sich diese Krankheitszustände im Zusammenhang mit parenteralen Infektionen entwickelt hatten, regelmässig im Magen und Zwölffingerdarm Colibazillen vorkamen, während sie dort bei gesunden oder an chronischen Ernährungsstörungen oder sonstigen Krankheiten leidenden Kindern fehlten. Die Ansichten von der Rolle, welche diese sog. endogene Darminfektion bei der Entstehung der Dyspepsie und Intoxikation spielt, sind sehr geteilt. Einige Forscher betrachten sie bloss als eine sekundäre Erscheinung (FINKELSTEIN u. a.), andere sprechen ihr nur die Bedeutung zu, dass jene sich in den oberen Darmabschnitten entwickelnden Colibazillen, Toxine (PLANTENGA, BESSAU u. a.) oder Amine (MORO, ROSKE, RÖTHLER, MANICATIDE u. a.) erzeugen, welche durch

die Darmwand hindurch absorbiert werden und Vergiftungssymptome verursachen; drittens ist noch die Ansicht vertreten, dass es sich um eine spezifische, von aussen hergekommene Infektion handle. Die letztgenannte Ansicht wird von ADAM umfasst, der in Zwölffingerdarm bei Dyspepsie und Intoxikation gefundene Colibazillen untersucht und bei ihnen besondere biologische Eigenschaften festgestellt hat. Diese Dyspepsiecolibazillen ADAMS gleichen den bei Kälberruhr angetroffenen Colibazillen und haben sich in Tierversuchen virulent gezeigt. Nach der Ansicht von KLEINSCHMIDT u. a. spielen ADAMS Dyspepsiecolibazillen eine grosse Rolle in der Pathogenese der Dyspepsie. WEISE konnte indessen mit Hilfe der Tierpassage gewöhnliche Colibazillen den Dyspepsiecolibazillen ähnlich machen; und SCHEER und ABRAHAM, welche zwar zugeben, dass die in Fällen von Dyspepsie und Intoxikation gefundenen Colibazillen virulenter als andere sind, vermochten durchaus nicht immer, bei den von ihnen angetroffenen Bakterien die von ADAM erwähnten biologischen Eigenschaften nachzuweisen. DENECKE fand die ADAMSchen Dyspepsiecolibazillen nicht pathogener als andere gewöhnliche Colibazillen. GOLDSCHMIDT glaubte die ADAMSchen Bakterien mit Hilfe der Agglutination genauer definieren zu können, obwohl die allermeisten Forscher (ESCHERICH, PFAUNDLER, BESSAU, ASCHENHEIM und HOLSTEIN, KRAMÁR, BERMAN, RYTI u. a.) auf Grund wiederholter Untersuchungen zu dem Resultat gekommen sind, dass die Bestimmung der Colibazillen mit Hilfe der Agglutination unmöglich ist. Es kann festgestellt werden, dass die Forscher, welche die akute Dyspepsie und Intoxikation für eine durch spezifische Bakterien hervorgerufene Krankheit halten, noch nicht imstande gewesen sind, die Richtigkeit ihres Standpunktes bindend zu beweisen.

Die endgültige Entscheidung dieser Frage wäre jedoch von äusserstem Gewicht, weil die uns zur Verfügung stehenden Behandlungsmittel in betreff dieser Krankheit noch recht mangelhaft und von unsicherer Wirkung sind. Erst dann, wenn diese Frage klargestellt ist, könnte man etwa in Betracht kommende spezifische Behandlungsmethoden sachlich entwerfen



und begründen; bis jetzt hat man es mehr als Experiment und aus Mangel an etwas besserem mit verschiedenen Sera und Vakzinen versucht (PLANTENGA, SCHEER und ABRAHAM u. a.), deren Ergebnisse auf die Wirkungen unspezifischer Eiweisstoffe zurückgeführt werden können. Infolgedessen fand ich es angebracht, Untersuchungen über diesen Gegenstand anzustellen, und führte vor einigen Jahren eine Arbeit aus, in der ich vor allem folgende Punkte klarzustellen suchte:

1. Findet man auch hierzulande in Fällen von Dyspepsie und Intoxikation ADAMS Dyspepsiecolibazillen?

2. Ist es möglich, mit irgendeiner anderen serologischen Reaktion besser als mit der Agglutination die in betreff ihrer biologischen Eigenschaften zu verschiedenen Gruppen gehörenden Colibazillen zu definieren?

Ich isolierte Bazillenstämme aus dem Urin von einem an Colipyelitis, aus den Fäzes von 3 an Intoxikation und 9 an Dyspepsie erkrankten Kindern, in den Intoxikationsfällen auch aus dem Mageninhalt, sowie aus den Fäzes von 2 gesunden Flaschenkindern und 2 gesunden Brustkindern; im ganzen 89 Stämme. Die biologischen Eigenschaften dieser Stämme untersuchte ich hinsichtlich verschiedener biologischer Reaktionen und verschiedener Zucker- und Alkoholspaltungen, unter diesen auch aller zur Definition der ADAMSchen Bazillen erwähnten, und konnte die Stämme auf Grund dieser Reaktionen in Haupt- und Untergruppen einteilen.

Mein Material war zwar so klein, dass es keine endgültigen Schlussfolgerungen erlaubt, *doch legen meine Ergebnisse ebenso wie diejenigen von RYTI u. a. dar, dass man die Colibazillen nicht auf Grund ihrer bakteriologischen Merkmale einheitlich gruppieren kann; es scheint auch nicht möglich zu sein, wie in der pädiatrischen Literatur immer wieder von neuem behauptet wird, nach den von ADAM aufgeführten biologischen Merkmalen einen spezifischen Dyspepsiecolibazillus zu definieren.*

Wie schon erwähnt, hat es sich in zahlreichen Untersuchungen als unmöglich erwiesen, die verschiedenen biologischen Gruppen des Colibazillus mit Hilfe der Agglutination zu unterscheiden, und diese Reaktion ist auch nicht zum Nachweis der

durch Coliinfektionen hervorgerufenen Agglutinine verwendbar. Dasselbe ergab sich bei der Untersuchung des Colibazillus und der von ihm erzeugten Immunkörper mit Hilfe der Komplementbindungsreaktion (AMIRADZIBI, ALTMAN und RAUTH u. a.). Die Bakterienkonglutinationsreaktion von STRENG hat sich in betreff vieler verschiedener Bakterien als eine sehr scharfe Reaktion erwiesen. In bezug auf die Dysenterie z. B. liefert sie deutlich bessere Resultate als die Agglutination und die Komplementbindungsreaktion (FITZGERALD, LUCAS und SCHÖRRER). MURTO fand in Fällen von Typhus und Paratyphus B die Konglutination besser als die Agglutination. Er untersuchte auch das Verhalten des Colibazillus bei der Konglutinationsreaktion und stellte fest, dass ein Colistamm einen spezifischen Immunkörper erzeugte.

Ich unternahm es, zu untersuchen, ob es möglich wäre, mit Hilfe der Konglutinationsreaktion die von mir gezüchteten Colibazillenstämme genauer zu bestimmen und zu gruppieren. Für diese Versuche stellte ich 10 Immunsera mit 6 saccharosepositiven Stämmen her. Mit diesen Sera und mit allen obenerwähnten Bazillenstämmen führte ich Konglutinations- und Agglutinationsversuche aus. *Die Ergebnisse stützen die Auffassung, dass zwischen den Agglutinations- und Konglutinationsreaktionen ein wesentlicher Unterschied besteht, obwohl man nicht auf Grund meiner Untersuchungen entscheidendere Schlüsse in bezug auf dieses äusserst interessante und bisher unklare theoretische Problem ziehen kann.*

*Ausserdem ging aus meinen Konglutinationsversuchen folgendes hervor: Obwohl mit den von mir untersuchten Colistämmen die Konglutination bedeutend öfter als die Agglutination positiv ausfiel, so vermag man doch nicht einmal mit Hilfe der Konglutinationsreaktion voneinander deutlich abweichende Colibazillengruppen zu definieren. Daher ist es auch nicht denkbar, auf die Konglutinationsreaktion gestützt, zu klinischen Zwecken brauchbare Resultate zu erzielen, die geeignet wären, die Ätiologie der Dyspepsie und der Intoxikation zu klären. — Über die Einzelheiten verweise ich auf meine Arbeit in Acta Soc. Med. Fenn. 1936.*

Bei den oben referierten Versuchen habe ich noch nicht untersucht, inwieweit mit bakteriolytischen Versuchen bessere Ergebnisse zu erzielen seien. Diese Reaktion wird ja in der Praxis zur Unterscheidung von einander nahe stehenden Bakterien gebraucht (KOLLE—HETSCH). BESSAU, ROSENBAUM und LEICHENTRITT sprechen auch den Gedanken aus, dass die Bakteriolytine besser als die Agglutinine dem Antikörperprodukt der Endotoxine entsprechen, sie haben sich jedoch wegen des schwierigeren Nachweises jener mit Agglutinationsversuchen begnügt. Ich habe jetzt meine Untersuchungen in dieser Hinsicht durch folgende Versuche ergänzt:

Zu meinen Versuchen benutzte ich Kaninchen-Immunsera, zu deren Herstellung ich Kaninchen mit den bei meinen früheren Untersuchungen isolierten Colibazillenstämmen Nr. II,37 und Nr. II,54 und mit einem Colistamm Nr. 26, den ich i. J. 1942 aus dem Magen eines an Intoxikation erkrankten Kindes isolierte, folgenderweise immunisierte:

#### *Kaninchen 1.*

16.6.43.	0,5 ccm intravenös, Bakterienstamm Nr. II,37	
21.6.43.	1,0 » » »	
26.6.43.	1,5 » » »	
6.7.43.	Blutentnahme	Serum I
18.8.43.	$\frac{1}{10}$ Öse intraperitoneal, Bakterienstamm Nr. II,37	
26.8.43.	Blutentnahme	Serum I,2
21.9.43.	$\frac{1}{2}$ Öse intraperitoneal, Bakterienstamm Nr. II,37	
1.10.43.	Blutentnahme	Serum I,3

#### *Kaninchen 2.*

16.6.43.	0,5 ccm intravenös, Bakterienstamm Nr. II,54	
21.6.43.	1,0 » » »	
26.6.43.	1,5 » » »	
6.7.43.	Blutentnahme	Serum II

#### *Kaninchen 3.*

18.8.43.	$\frac{1}{10}$ Öse intraperitoneal, Bakterienstamm Nr. II,54	
26.8.43.	Blutentnahme	Serum III
21.9.43.	$\frac{1}{2}$ Öse intraperitoneal, Bakterienstamm Nr. II,54	
1.10.43.	Blutentnahme	Serum III,2

#### *Kaninchen 4.*

18.8.43.	$\frac{1}{10}$ Öse intraperitoneal, Bakterienstamm Nr. 26.	
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26.8.43.	Blutentnahme	Serum IV
28.8.43.	$\frac{1}{2}$ Öse intraperitoneal, Bakterienstamm Nr. 26	
16.9.43.	Blutentnahme	Serum IV,2
21.9.43.	1,0 Öse intraperitoneal, Bakterienstamm Nr. 26	
1.10.43.	Blutentnahme	Serum IV,3

Zu den intravenösen Einspritzungen wurden folgende Emulsionen gebraucht: von einer 24 Std. bei 37° C gewachsenen gewöhnlichen Schrägagarkultur wurden die Bazillen mit 5 ccm physiol. Kochsalzlösung emulgiert, danach  $\frac{1}{2}$  Std. bei 56° C erwärmt.

Intraperitoneal wurden lebendige Bazillen aus einer 24 Std. bei 37° C gewachsenen gewöhnlichen Schrägagarkultur eingespritzt.

Nach den Einspritzungen frassen die Tiere ein paar Tage schlecht, waren aber sonst nicht krank.

Die Sera wurden  $\frac{1}{2}$  Std. bei 56° C inaktiviert.

Mit diesen Sera führte ich bakteriolytische Versuche mit den drei zur Immunisierung benutzten Bazillensstämmen aus und ausserdem noch mit einem Paracolistamm, den ich aus der durch Lumbalpunktion erhaltenen Cerebrospinalflüssigkeit eines 2 Monate alten, an purulentem Meningitis erkrankten Kindes isolierte.

Die Versuche wurden mit folgenden Kombinationen ausgeführt. (Die Nummer des dem Serum entsprechenden Bazillensstammes ist kursiviert.)

Serum I	Bazillensstamm	<i>II,37</i> und <i>II,54</i>
» I,2	»	<i>II,37</i> , <i>II,54</i> und 26
» I,3	»	<i>II,37</i> , <i>II,54</i> , 26 und Paracoli.
» II	»	<i>II,37</i> , <i>II,54</i>
» III	»	<i>II,37</i> , <i>II,54</i> und 26.
» III,2	»	<i>II,37</i> , <i>II,54</i> , 26 und Paracoli.
» IV	»	<i>II,37</i> , <i>II,54</i> und 26.
» IV,3	»	<i>II,37</i> , <i>II,54</i> , 26 und Paracoli.

Aus praktischen Gründen konnte ich PFEIFFERSche Versuche, die ja bei den bakteriolytischen Untersuchungen die beste Methode ist, nicht ausführen, sondern führte meine Versuche in vitro mit dem sog. bakteriziden Plattenverfahren in folgender Weise aus.

Nr.	Bakt. kultur 1/5000	Serum in 0,5 physiol. Kochsalzlösung		Frishes Kaninchen-serum 1/10	Physiol. Kochsalz-lösung	
1.	0,5	Immunserum	1/100 cem	0,5	—	3 Std. in 37° C, danach gegossen
2.	0,5	»	1/500 »	0,5	—	»
3.	0,5	»	1/1000 »	0,5	—	»
4.	0,5	»	1/10000 »	0,5	—	»
5.	0,5	»	1/20000 »	0,5	—	»
6.	0,5	»	1/30000 »	0,5	—	»
7.	0,5	»	1/40000 »	0,5	—	»
8.	0,5	»	1/50000 »	0,5	—	»
9.	0,5	»	1/100000 »	0,5	—	»
10.	0,5	»	1/200000 »	0,5	—	»
11.	0,5	Normalserum	1/100 »	0,5	—	»
12.	0,5	»	1/1000 »	0,5	—	»
13.	0,5	»	1/10000 »	0,5	—	»
14.	0,5	—	—	0,5	0,5	»
15.	0,5	Immunserum	1/100 cem	—	0,5	»
16.	0,5	Normalserum	1/100 »	—	0,5	»
17.	—	—	—	0,5	1,0	»
18.	—	Immunserum	1/100 cem	—	1,0	»
19.	—	Normalserum	1/100 »	—	1,0	»
20.	0,5	—	—	—	1,0	»
21.	0,5	—	—	—	1,0	sofort gegossen

Als Bakterienemulsion diente eine in gewöhnlicher Bouillon während 24 Std. in 37° C gewachsene Kultur in einer Verdünnung von 1/5000 und als Komplement frisches Kaninchenserum.

Die Ergebnisse der Versuche waren im grossen und ganzen negativ. Nur in einigen homologen Kombinationen war eine schwache bakteriolytische Wirkung feststellbar, die aber auch hauptsächlich auf dem Gebiete der stärkeren Serumkonzentrationen vorkam, so dass sie durch die Normalbakteriolyse hervorgerufen sein kann. Darauf weist auch die bei der homologen Kombination III,2—II,54 vorgekommene ziemlich starke

Reaktion hin, deren spezifische Bedeutung dadurch zweifelhaft wurde, dass bei diesem Versuch das Normalserum eine entsprechende Reaktion ergab. Bei einer einzigen heterologen Kombination, IV,3—II,54, war eine schwache Bakteriolyse feststellbar, aber auch in diesem Falle erschien beinahe dieselbe Reaktion mit dem als Kontrolle benutzten Normalserum.

Aus diesen Versuchen wird zu schliessen sein, dass die von mir aus Dyspepsie und Intoxikationsfällen der Säuglinge isolierten Colibazillenstämme mit in vitro ausgeführten bakteriolytischen Untersuchungen nicht genauer zu bestimmen und zu gruppieren sind. — Ich hielt es nicht für begründet, meine Versuche auf eine grössere Anzahl Bazillenstämme zu erstrecken, denn der obengenannte Schluss wäre kaum nennenswert geändert worden, wenn einige Stämme auch positive Resultate ergeben hätten.

Bei den negativen Ergebnissen lag der Gedanke nahe, dass sie vielleicht durch eine missglückte Immunisierung bedingt seien. Deshalb unternahm ich eine Kontrolluntersuchung; ich führte mit allen meinen Sera und mit allen vier Bakterienstämmen Konglutinations- und Agglutinationsversuche aus und zwar mit derselben Methode wie in meinen früheren Untersuchungen. Bei diesen Versuchen erwiesen sich die Sera bei den Konglutinations- und Agglutinationsreaktionen durchaus wirksam. In den meisten homologen Kombinationen waren beide Reaktionen deutlich und stark positiv, in einigen war bloss eine Reaktion positiv; unter den heterologen Kombinationen gab es einige Fälle, in denen beide positiv waren, und andere, in denen die Konglutination positiv, die Agglutination negativ war und umgekehrt. Diese kleine Versuchsreihe ergab im allgemeinen ein ähnliches Bild, wie das grössere Material in meiner vorigen Arbeit. Daraus ist zu schliessen, dass die negativen Ergebnisse bei den bakteriolytischen Versuchen nicht auf einer missglückten Immunisierung beruhten.

Aus allen meinen oben dargelegten Untersuchungen kann also geschlossen werden, dass die bei der Dyspepsie und Intoxikation der Säuglinge vorkommenden Colibazillen weder auf Grund der biologischen Eigenschaften noch durch verschiedene gewöhnliche

*serologische Untersuchungsmethoden spezifisch zu gruppieren sind.* Hieraus folgt, dass die durch Colibazillen und seine Toxine verursachten Dyspepsie- und Intoxikationsfälle von den eventuell durch irgendwelche andere Bazillen verursachten Fällen mit diesen Methoden nicht klinisch zu unterscheiden sind.

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FROM THE CHILDREN'S DEPARTMENT OF THE CENTRAL HOSPITAL,  
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## **The haemoglobin and erythrocyte values during the 1st year of life following different methods of clamping of the umbilical cord.**

By

**PER SELANDER.**

### **Introduction.**

Since the last decades of the 19th century the blood of the infant, and in particular that of the newborn child, has been the object of a large number of investigations. It is undeniably odd that the results the different investigators have reached as to the normal red-blood picture during infancy are so unlike one another. Differences of this kind dating from before the 1920's can be blamed on faulty technique. Nevertheless, though many investigations have been made with impeccable technique since this time, 'normal values' have been variously communicated which differ from one another — sometimes, indeed, to a high degree. Earlier authors who have had to do with this problem have, needless to say, criticised this fact. The attempts, hitherto made, to determine the normal red-blood picture of the infant force one to the conclusion that the same technique in different hands gives considerably varied values, even among children not noticeably differing from one another either socially or in respect of race. This is particularly true of the haemoglobin determinations.

A pertinent problem is the time for clamping of the umbilical cord. It has been discussed whether it is more suitable from the point of view of the infant to clamp the cord early or late. Older literature has authors deprecating the latter practice; modern tendencies are, rather, the reverse.

Another much discussed problem is how far different times for clamping of the cord affect the blood picture. It is not impossible that we have here a source of error in the experiments to determine the normal red-blood picture of the infant. This paper submits the result of an investigation of the red-blood picture at different times for clamping of the umbilical cord. Before reviewing the literature on similar investigations made earlier on, the author will make a survey of some more recent investigations into the amount of blood in the placenta and the umbilical cord, and also into the amount of blood of the newborn child.

### Survey of the literature.

The seemingly most important investigation into how much blood passes from the umbilical cord and the placenta to the child after birth has been made by HASELHORST and ALLMELING (1930). They weighed 120 infants at birth and determined how much the infants with unclamped cords increased in weight from immediately after birth to the expulsion of the placenta: i. e. how much blood the children received after birth. After 1 minute the infants increased, on an average, 50 gm, after 3 minutes 71 gm, after 15 minutes 95 gm, and after 30 minutes 98 gm.

KRAMANN and HOFFMANN (1939) have investigated how much blood can be extracted from the umbilical cord and the placenta according as the cord is squeezed out towards the child or towards the placenta before being knotted. In the former case an average of 3 gm could be extracted after clamping in 200 investigated cases. If, on the other hand, the cord was squeezed out towards the placenta, an average of 108 gm was yielded in an equally large group. This latter method, then, which is of course not physiological, supplied the child with about 10—15 gm more blood than if the placenta were left to come away spontaneously.

As the pulsations in the umbilical cord usually cease within 3 minutes, the advantage of waiting to clamp it till this happens is that the infant is supplied with about 70 gm of blood. If one waits until the placenta is expelled, which usually

takes place within 10—15 minutes, there is a further gain of about 20 gm of blood. Extra manipulations with the cord may even mean yet another 10—15 gm or so of blood for the infant.

As regards the amount of blood in a new-born infant, ROBINOW and HAMILTON (1940) have found it to constitute on an average  $9.8 \pm 0.87\%$  of the body-weight. BRINES and GIBSON (1941) found a blood volume of between 250—300 cc in full-term, normal infants. It cannot, however, be seen from these investigations whether the umbilical cord was clamped late or early; the time this is done must nevertheless be an important factor in determining the normal blood volume.

All the same, the volume of the full-term, new-born infants' blood can probably be estimated, according to these investigations, at about 250—350 gm. Different methods of detaching the umbilical cord may thus cause the amount of blood to vary by about  $\frac{1}{4}$ , perhaps even  $\frac{1}{3}$ .

The question is, therefore, whether this affects the infants' health.

HASELHORST and TRAUTVETTER (1929) investigated the blood of 50 fullterm children (weight at birth more than 2 500 gm) whose umbilical cord had been clamped immediately after birth, and in as many more where it had been clamped after about 5 minutes. After 16—18 hours the mean number of erythrocytes in the first group was 5.48 millions, and in the second group 6.76 millions. (No statistical calculation has been made.) They submitted no haemoglobin determinations. It consequently seems as if the children with cords clamped late had a greater number of erythrocytes than those detached early. — HASELHORST and TRAUTVETTER have obtained remarkably high values from certain of the children detached late, not infrequently over 8 millions; the maximum was 8.8 millions, indicating that the technique was not perfect.

KRAMANN and HOFFMANN (1939) made haemoglobin and erythrocyte determinations in the investigation mentioned above. The infants who received an increased supply of blood by a squeezing out of the umbilical cord towards the child had on the first day of life 18 % higher haemoglobin values

and 19 % higher erythrocyte values. On the 5th day the corresponding figures were 17 % and 16 % respectively, and on the 9th day 17 % and 15 %.

The above authors did not extend the investigation beyond the neonatal period.

WINDLE and co-workers have submitted results for the years 1940—41 of blood investigations of infants whose umbilical cords were clamped at different points in time. In 25 cases the cord was clamped as soon as possible after birth. A time of 30 seconds is given for 7 children, and of 0 seconds for the remainder. In 25 other children the cord was not clamped until the placenta had begun to descend into the vagina. During the whole of the first week of life the children whose umbilical cord had been cut late had distinctly higher haemoglobin and erythrocyte values. Those detached early had on an average 19.5 gm (125 %) haemoglobin and 5.45 million erythrocytes. Those detached late had on an average 22.1 gm (142 %) haemoglobin and 6.01 million erythrocytes. The difference is statistically significant. At an age of 8—10 months, 15 children who had been detached early showed on an average  $10.8 \pm 1.9$  gm (69 %) haemoglobin and  $5.06 \pm 0.86$  million erythrocytes. Of those detached late 13 were investigated at the same point in time. They had  $11.9 \pm 1.3$  gm (76 %) haemoglobin and  $4.45 \pm 0.80$  million erythrocytes. The fact that the erythrocytes showed a higher value in the group where the cord was clamped early — that is to say, rather the opposite of what one would expect — is taken by WINDLE and co-workers to indicate a deficiency of iron. But as the investigated children are few one would hardly be justified in drawing any definite conclusion from these figures. Nor does any statistical difference between the different groups appear. (The difference is  $1.1 \pm 2.3$  gm haemoglobin, and  $0.61 \pm 0.92$  million erythrocytes.)

As regards the last-mentioned authors' investigations, the clamping of the cord so soon after birth in the one group must be looked upon as very unphysiological. It would scarcely be surprising, then, to find differences in the two groups.

These hitherto published works<sup>1</sup> seem to warrant the conclusion that a delayed clamping of the umbilical cord makes for an increased volume of blood in the infant, and also gives higher haemoglobin and erythrocyte figures during the first week of life. Investigations of representative material do not extend further. The literature gives no information as to whether the increased amount of blood resulting from a late clamping of the cord has any favourable effect on the health of the infant after the neonatal period.

The present study aims at getting some idea of the haemoglobin and erythrocytes during the first year of life in infants whose umbilical cords were clamped according to different methods. It also tries to discover whether any influence from these different methods can be traced in the infants' health. On the other hand it was not the author's intention to attempt to determine the normal values in infants, since investigations of this kind have fairly recently been carried out in Sweden by MAGNUSSON (1935) both on full-term and premature infants, and by FAXÉN (1937) on full-term infants. The present author's investigations have nevertheless been made with such meticulous technique and the material is so large that conclusions as to the normal values at this age may well be justified. Such conclusions will also be discussed, therefore.

### Author's investigations.

*Material.* All the children investigated were born in the maternity department of this hospital.<sup>2</sup> The material excludes all children weighing less than 2500 gm at birth, children delivered with forceps, children with haemorrhages, injured children and children delivered by Caesarean section. In the

<sup>1</sup> The present situation has made it difficult to procure literature, so that the review cannot claim to be complete.

<sup>2</sup> To the former Chief of the maternity department, Dr. G. PALLIN, M. D., who most kindly allowed me to carry out these investigations, I beg to offer my warm thanks.

remaining cases attempts have been made to clamp the cord immediately after birth and after the expulsion of the placenta alternately, during different periods, or else to clamp it when the pulsations ceased and immediately, alternately. It has, however, proved hard for various reasons to carry out a consistent method of alternation. In any case there has certainly been no selection. As preliminary investigations showed that when the cord was clamped immediately the children got plainly lower blood values this method was stopped, as it was considered that sufficient material had been obtained. It has not upset either mother or child to any great degree to wait to clamp the cord until the placenta has been expelled, which usually happened after 10—15 minutes. The pulsations in the cord usually cease within 3 minutes. In the immediately-detached group the time for clamping of the cord is about 1 minute. The time of 0 seconds have not been considered desirable, since there was a risk of injuring the child with a method of this kind.

For the first week of life the blood investigations were made in the maternity department. In the subsequent investigations only those children could come into question who could be followed at the Children's Welfare Centre, of which the author himself is in charge. The blood samples were taken from these children when they were brought for consultation. The investigation after the first week of life also included the children who had got diseases of different kinds; this is no other than right, since different methods of clamping of the umbilical cord may, of course, be thought to cause diseases, which in their turn affect the red-blood picture. Moreover, the investigation is intended to find out the state of health in the different groups. When the samples of blood were taken the children were well, needless to say. Both breast-fed children and those fed on cow's milk formulas were included. All children received vitamin D from October to May from the age of about 2 months, and foodstuff containing vitamin C from the age of about 3  $\frac{1}{2}$  months. As the author himself

superintended all children, it has been possible to guarantee that none of them received medicine containing iron.

*Methods.* The investigations were made on the 1st, 3rd and 7th day of life, and in the 2nd, 3rd, 6th and 12th month. One investigator (trained laboratorian) took all samples of blood and made all the determinations. She did not know in which way the cord had been clamped. The samples were taken from the finger-tip; the first drop was wiped away. From the puncture 2 samples were taken for haemoglobin and 2 for erythrocytes. For the haemoglobin determinations 2 Zeiss-Ikon haemometers were used, standardized every 4 months according to VAN SLYKE's method in the laboratory of the SAHLGREN medical department II (Dr. ODIN). They showed completely tallying values. HADEN's standard (15.6 gm = 100 %) was used in calculating the correction figure for the haemoglobin %. The values used are the mean of 2 readings of each of the 2 samples. All samples were read off in day-light. For the determination of the erythrocytes BÜRKER's chamber was used. 16 C—D squares were counted for each sample, and the values used constitute the mean of the count for the 2 samples.

The material presented here has been treated statistically, using customary formulas.

### **The haemoglobin and erythrocyte values during the first week of life.**

Table 1 shows the *haemoglobin* values obtained. It is seen from the table that, during the first week of life, the longer the clamping of the umbilical cord is delayed the higher the haemoglobin percentage. The difference between Group I (clamped immediately) and Group III (clamped after the expulsion of the placenta) is statistically significant for every investigated day. (Diff.  $7.3 \pm 1.86$ ,  $9.6 \pm 1.86$  and  $8.2 \pm 1.71$  %.) If Group I is compared with Group II (clamped after the pulsations ceased) the values in the latter group are numeri-





cally higher, but only on the 7th day is there a statistically significant difference ( $6.4 \pm 2.10\%$ ). If Groups II and III are compared, numerically higher values are similarly found for each investigated day in Group III, but only for the 3rd day is it likely that there is a statistical difference ( $5.7 \pm 2.14$ ).

Table 2 contains the *erythrocyte* values. Here, too, there is during the first week of life a statistically significant difference between Group I and Group III, with higher values for each investigated day in the latter group. (Diff.  $0.37 \pm 0.107$ ,  $0.32 \pm 0.102$ , and  $0.27 \pm 0.094$  millions.) A comparison of Groups I and II yields a statistically significant difference on the 1st and 7th day (Diff.  $0.63 \pm 0.110$  and  $0.40 \pm 0.112$  millions) but not with certainty on the 3rd day, however. A comparison of Groups II and III, on the other hand, yields no significant difference. On the first day there are probably higher values in Group II this is without doubt merely an indication of how difficult it is to obtain exact values with the technique used.

These investigations, consequently, make it plain that a delayed clamping of the umbilical cord makes for higher haemoglobin and erythrocyte values during the first week of life. The differences are, however, not so great as reports in the literature might lead one to expect. To produce significant differences both for haemoglobin and erythrocytes those methods of clamping of the cord must be used which differ most from one another. It is, however, to be noted that the author did not clamp the cord as soon as WINDLE and co-workers, nor did he use the manipulations with the cord which KRAMANN and HOFFMANN are reputed to have done, both of which methods are equally unphysiological. The author's methods can be taken as those commonly used. It is seen from the investigation that the difference between methods I and II is larger than between II and III.

#### **The haemoglobin and erythrocyte values after the first week of life.**

Table 1 also contains the *haemoglobin* values in the 2nd, 3rd, 6th and 12th month. There is not in any month any significant difference between any of the groups, not even

*Tab. 2.*  
Erythrocyte values during the 1st year of life in full-term infants with different times for clamping of the umbilical cord.

Methods of clamping of the umbilical cord									
Age	Group I. Immediately			Group II. When the pulsations ceased			Group III. After expulsion of the placenta		
	Erythrocytes (million)		No. of observations	Erythrocytes (million)		No. of observations	Erythrocytes (million)		
	average $\pm$ mean error	standard deviation $\pm$ mean error		average $\pm$ mean error	standard deviation $\pm$ mean error				
	1. day . . .	5.51 $\pm$ 0.077	0.76 $\pm$ 0.064	50	6.14 $\pm$ 0.079	0.76 $\pm$ 0.056	97	5.88 $\pm$ 0.074	0.73 $\pm$ 0.052
3. " . . .	5.43 $\pm$ 0.077	0.77 $\pm$ 0.055	53	5.68 $\pm$ 0.087	0.64 $\pm$ 0.062	96	5.76 $\pm$ 0.075	0.74 $\pm$ 0.059	
7. " . . .	5.24 $\pm$ 0.066	0.63 $\pm$ 0.047	48	5.64 $\pm$ 0.091	0.63 $\pm$ 0.064	91	5.51 $\pm$ 0.067	0.64 $\pm$ 0.047	
2. month . . .	3.95 $\pm$ 0.025	0.14 $\pm$ 0.017	41	3.98 $\pm$ 0.074	0.54 $\pm$ 0.060	51	4.12 $\pm$ 0.092	0.65 $\pm$ 0.065	
3. " . . .	3.99 $\pm$ 0.055	0.32 $\pm$ 0.039	45	4.02 $\pm$ 0.059	0.40 $\pm$ 0.042	61	4.02 $\pm$ 0.059	0.46 $\pm$ 0.042	
6. " . . .	4.22 $\pm$ 0.066	0.34 $\pm$ 0.047	48	4.13 $\pm$ 0.040	0.27 $\pm$ 0.028	53	4.15 $\pm$ 0.055	0.40 $\pm$ 0.039	
12. " . . .	4.35 $\pm$ 0.092	0.49 $\pm$ 0.065	39	4.32 $\pm$ 0.056	0.35 $\pm$ 0.040	52	4.42 $\pm$ 0.071	0.51 $\pm$ 0.050	

between the two extreme methods of clamping of the cord. There is not even a tendency towards increase in the groups of later times for clamping of the cord; this implies that there would not be any difference in a larger material, either.

Table 2 shows the *erythrocyte* values during the same months. Here, too, there is no significant difference — possibly a tendency towards one in the two extreme methods, but no definite conclusion can be drawn from these numerical differences.

The investigation has shown, then, that higher haemoglobin and erythrocyte figures occur in the first week of life if the clamping of the cord is delayed. But when the children are examined in the 2nd month these differences have already disappeared, not to appear again.

### Discussion of the result.

Now one may wonder why those children who receive more blood from the cord and the placenta have higher haemoglobin and erythrocytes values at all. Earlier investigations show this is not due to higher haemoglobin and erythrocyte values in the blood of the umbilical cord. WAUGH and co-workers (1939) found 15.36 gm (98 %) haemoglobin in this latter blood, and 15.46 gm (99 %) in sinus blood, and it is a known fact that, in new-born children, venous blood gives distinctly lower values than capillary blood (VAHLQUIST 1941, and others). WINDLE and co-workers (1940—1941) found 15.7 gm (101 %) haemoglobin and 4.5 million erythrocytes in blood from the umbilical cord, but in blood from the heel they found between 18.9 and 21.3 gm (121—135 %) haemoglobin, and between 5.57 and 5.93 million erythrocytes, depending on different methods of clamping of the cord. The simplest explanation is surely that the increased influx of blood gives a volume that is relatively too large for the new-born child. The blood volume is rapidly normalized by the removal of water or, more probably, plasma, from the stream. The destruction of the erythrocytes does not take place at the same rate. An old investigation by HOFMEIER

and co-workers (cit. HASELHORST and TRAUTVETTER 1929) shows this may be so; the work demonstrates that children with cords cut late have larger quantities of urine during the first days of life than do other children. After the neonatal period the erythrocyte values and the blood volume adjust themselves, the differences between the different methods of clamping the cord thus disappearing.

But the child does also get iron from the increased amount of blood from the placenta. According to the investigations of HASELHORST and ALLMELING (1930) the children in the present author's Group I should have got about 50 gm, in Group II about 70 gm, and in Group III about 95 gm of blood after birth. Compared with Group I, therefore, the method in Group II gives an extra 20 gm of blood, and the one in Group III an extra 45 gm. As 100 gm of placental blood contains about 56 mgm of iron (WINDLE 1941), the children in Group II have received about 11 mgm more iron than Group I, and Group III about 25 mgm more iron than Group I. The total iron content of the new-born child has been calculated to be about 350 mgm. The difference between the extreme groups in the author's investigation is therefore that the children whose cords were cut last have about 7 % more iron than those cut earliest. Judging from the investigation this addition is of no importance in so far as it is not sufficient to give demonstrably higher blood values during the first year of life, if one excludes the neonatal period. Consequently, infants who in the author's opinion have their umbilical cord clamped early seem to have iron in sufficient quantities.

#### **The state of health of the infants in the different groups of clamping the cord.**

It has only been possible to follow up those infants registered at the Welfare Centre. Their general condition has been good. No infant has died. All diseases have been registered, and all complaints with distinct symptoms have

probably been known to the author. Slight catarrhal infections have, of course, escaped registration, but this is of no importance for a comparison between different groups. When thus comparing diseases in the different groups only those affections have been included which may conceivably be due in some way to a diminished supply of blood to the newborn child. The diseases then in question are, needless to say, unspecific infections, dyspepsias, rickets, and so on, but not different kinds of rash, specific infections, and the like.

The collocation of data shows that, during the first year of life, 51 % of the 43 investigated infants in Group I had been ill, 51 % again of the 62 in Group II, and 56 % of the 70 in Group III. Thus, no significant difference appears between the different groups. So that no indication can be obtained from this method, either, that any certain advantage accrues to the infant's health if clamping is delayed from about 1 minute until the placenta is expelled.

#### **Normal values of haemoglobin and erythrocytes during the first year of life.**

MAGNUSSON (1935) has investigated haemoglobin and erythrocytes during the first year of life in Swedish children, both premature (weighing less than 2 500 gm at birth) and full-term (weighing over 3 000 gm at birth). The blood samples were taken from the heel, after the foot had been warmed and massaged. His technique is not otherwise remarkably different from the one used by the present author. MAGNUSSON has not submitted any investigation of full-term children during the first week of life. It is generally stated in the literature that there is no significant difference in the haemoglobin and erythrocyte figures during the first week of life in premature and full-term children; the author has therefore used MAGNUSSON's premature children as material for comparison for this point in time. His material also includes those children who have at some time been ill, and those who were artificially fed.

FAXÉN (1937) has similarly investigated haemoglobin and erythrocytes in Swedish infants. These children weighed at least 3 000 gm at birth and were breast fed. In addition, only those children were included who had been well during the whole of the first year of life. The difference between FAXÉN's material and the author's is, then, that the author also included the children weighing down to 2 500 gm, those who had been artificially fed and also those who had been ill. Like the author, FAXÉN has taken the blood samples from the fingertip, and the technique has, on the whole, been the same. The same values for the period immediately after birth should be expected both in the author's and in FAXÉN's investigation, since the difference in the materials constituted by the weight at birth cannot affect the haemoglobin and erythrocyte determinations during the first week of life. On the other hand, somewhat lower values are to be expected after the neonatal period in the children investigated by the author, corresponding to the lowering of the blood content which artificially feeding and illness may be thought to occasion.

There are no data as to the time the umbilical cord was clamped in MAGNUSSON's and FAXÉN's works. It is therefore to be presumed that different methods were used in their material. As it may be supposed that the most usual way of clamping of the cord in Sweden is to wait, until the pulsations in the cord have ceased, the values of MAGNUSSON and FAXÉN correspond most nearly to the author's Group II. In a comparison between the blood values of MAGNUSSON, FAXÉN and the author, it would probably be quite justifiable to make the author's three values from each point in time into one group.

MAGNUSSON and FAXÉN have demarcated the ages of the children at the investigation by as short a period as a week, whereas the author has used a month. As, according to the investigations of these two authors, the haemoglobin and erythrocyte figures show considerably different values at different ages, particularly up to 3 months, there is a certain difficulty in comparing the different points in time. For this

reason a comparison can best be made on a diagram. A diagram like this is seen in fig. 1. The numerical values corresponding to the times investigated by the present author appear in table 3. FAXÉN gives his haemoglobin values in gm, which the author has turned into per cent.

Table 3 and fig. 1 show that the agreement between the *haemoglobin* values of the different investigators is not as

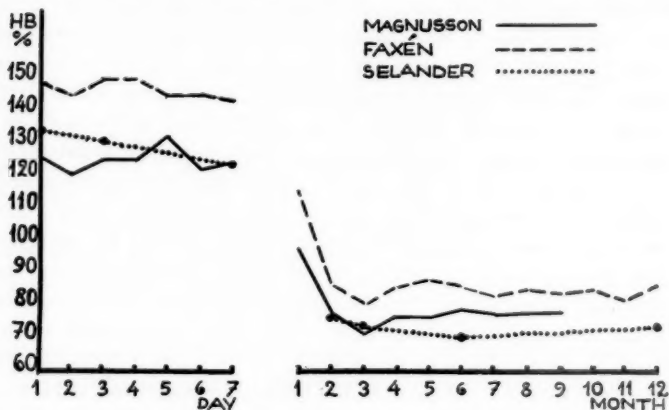


Fig. 1. Comparison between the haemoglobin % during the 1st year of life in 3 Swedish materials.

good as might have been expected from the similar materials and the, on the whole, similar technique. Broadly speaking, MAGNUSSON and the author have obtained the same values, whereas FAXÉN's are on another level. On the 3rd day of life FAXÉN's values are not less than 20–25 % higher, and at other time, too, they are usually 10–15 % higher.

Table 4 and fig. 2 show the *erythrocyte* values. As regards the first week of life the values of FAXÉN and the author tally very well, while MAGNUSSON's are lower. It should, however, be observed that the latter's material from this period consists of premature children. The difference may be due to the fact that the literature data as to the same values in premature and full-term children during the first week of

*Tab. 3.*  
Comparison between the haemoglobin % during the 1st year of life in 3 Swedish materials.

Age	MAGNUSON (1935)			FAXÉN (1937)			Present author	
	No. of observations	Haemoglobin in %		No. of observations	Haemoglobin in %		No. of observations	Haemoglobin in %
		average $\pm$ mean error	standard deviation $\pm$ mean error		average $\pm$ mean error	standard deviation $\pm$ mean error		average $\pm$ mean error
1. day . . . .	16	126.1 $\pm$ 4.8	10.2 $\pm$ 3.4	16	148.7 $\pm$ 1.60	6.4 $\pm$ 1.15	247	134.4 $\pm$ 0.88
3. » . . . .	17	125.0 $\pm$ 4.1	16.7 $\pm$ 2.9	16	150.0 $\pm$ 2.31	9.0 $\pm$ 1.60	249	130.6 $\pm$ 0.86
7. » . . . .	15	123.9 $\pm$ 3.2	12.2 $\pm$ 2.2	19	142.9 $\pm$ 3.33	14.7 $\pm$ 2.37	229	123.4 $\pm$ 0.80
2. month . . . .	38	79.4 $\pm$ 1.7	10.22 $\pm$ 1.2	65	86.5 $\pm$ 0.86	7.7 $\pm$ 0.71	125	76.9 $\pm$ 0.80
3. » . . . .	31	72.7 $\pm$ 1.2	6.52 $\pm$ 0.83	42	81.4 $\pm$ 0.83	5.8 $\pm$ 0.58	139	74.1 $\pm$ 0.48
6. » . . . .	23	79.4 $\pm$ 1.1	5.46 $\pm$ 0.80	42	85.9 $\pm$ 1.03	6.4 $\pm$ 0.71	128	70.1 $\pm$ 0.28
12. » . . . .	—	—	—	42	85.9 $\pm$ 1.09	7.1 $\pm$ 0.77	119	73.3 $\pm$ 0.46
								13.8 $\pm$ 0.62
								13.6 $\pm$ 0.61
								12.1 $\pm$ 0.56
								8.3 $\pm$ 0.56
								5.6 $\pm$ 0.34
								3.1 $\pm$ 0.20
								5.1 $\pm$ 0.33



*Tab. 4.*  
Comparison between the erythrocyte values during the 1st year of life in 3 Swedish materials.

Age	MAGNUSON (1935)			FAXÉN (1937)			Present author		
	No. of observations	Erythrocytes (million)		No. of observations	Erythrocytes (million)		No. of observations	Erythrocytes (million)	
		average $\pm$ mean error	standard deviation $\pm$ mean error		average $\pm$ mean error	standard deviation $\pm$ mean error		average $\pm$ mean error	standard deviation $\pm$ mean error
1. day . . . .	15	5.18 $\pm$ 0.17	0.57 $\pm$ 0.12	17	5.78 $\pm$ 0.130	0.54 $\pm$ 0.092	247	5.78 $\pm$ 0.050	0.79 $\pm$ 0.086
3. " . . . .	16	5.38 $\pm$ 0.18	0.74 $\pm$ 0.13	19	5.55 $\pm$ 0.122	0.53 $\pm$ 0.086	249	5.61 $\pm$ 0.048	0.75 $\pm$ 0.084
7. " . . . .	14	5.28 $\pm$ 0.20	0.77 $\pm$ 0.14	22	5.34 $\pm$ 0.127	0.50 $\pm$ 0.090	229	5.43 $\pm$ 0.043	0.65 $\pm$ 0.028
2. month . . .	15	4.25 $\pm$ 0.13	0.49 $\pm$ 0.089	66	3.91 $\pm$ 0.046	0.37 $\pm$ 0.033	125	4.03 $\pm$ 0.047	0.53 $\pm$ 0.034
3. " . . . .	18	3.93 $\pm$ 0.07	0.28 $\pm$ 0.047	44	3.96 $\pm$ 0.043	0.29 $\pm$ 0.030	139	4.01 $\pm$ 0.035	0.41 $\pm$ 0.025
6. " . . . .	15	4.86 $\pm$ 0.14	0.55 $\pm$ 0.10	42	4.57 $\pm$ 0.053	0.35 $\pm$ 0.037	128	4.16 $\pm$ 0.027	0.31 $\pm$ 0.019
12. " . . . .	—	—	—	42	4.58 $\pm$ 0.069	0.45 $\pm$ 0.049	119	4.37 $\pm$ 0.042	0.46 $\pm$ 0.030

life are incorrect. The haemoglobin values also indicate that this may be the case (table 3 and fig. 1). The haemoglobin for MAGNUSSON's premature children is lower than the author's, but for full-term children they are, on the other hand, higher. It may also well be that the umbilical cord of premature children is as a rule clamped more sooner than that of full-

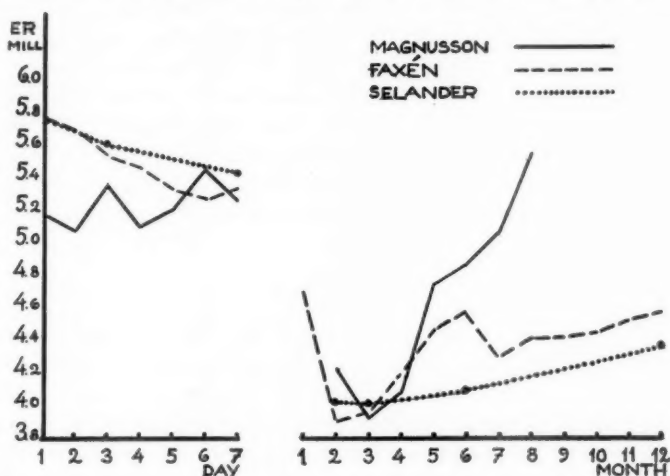


Fig. 2. Comparison between the erythrocyte values during the 1st year of life in 3 Swedish materials.

term children, and that this circumstance has affected MAGNUSSON's material. — Subsequently, the author's values are lower than FAXÉN's, but otherwise they agree very well. It is likely that the inclusion in the author's material of artificially fed children and those who have been ill has made for the lower values. MAGNUSSON's curve has a course completely different from that of the other investigators. Although MAGNUSSON's material is most like the author's, and should therefore be lower than FAXÉN's, he nevertheless shows the highest values.

In a comparison with other investigators this investigation, too, shows that much the same technique gives rather different blood values in infants. It is seen from table 1 that the

differences in the haemoglobin values between FAXÉN's and the author's material cannot be due to different methods of clamping of the cord. Even if this process be postponed until the placenta is expelled, the author gets nothing like so high values as FAXÉN. The only way in which these differences can be interpreted is that, in spite of all care, faults nevertheless find their way into the standardization of the haemoglobin apparatuses. For the present, therefore, haemoglobin investigations can only be assigned a relative value.

Taking into account the inclusion in the author's material of artificially fed children and those who have been ill, the erythrocyte values of FAXÉN and the author must be considered as agreeing well. It is difficult to find an explanation for MAGNUSSON's obtaining such high erythrocyte figures after the 4th month.

### Summary.

The author has investigated how the time for clamping of the umbilical cord influences haemoglobin, erythrocytes and state of health of full-term children during the first year of life. Both breast-fed and artificially fed children have been included in the material. The clamping of the umbilical cord have taken place as follows: 1) after about 1 minute from birth, 2) after the pulsations in the umbilical cord ceased and 3) after the expulsion of the placenta. The children have been investigated on the 1st, 3rd and 7th day of life, and in the 2nd, 3rd, 6th and 12th month. The result was the following:

1) If the cord is clamped late, the child gets higher haemoglobin and erythrocyte values during the 1st week of life. The time for clamping the cord is consequently of importance in the determinations of the normal red-blood picture of the new-born child.

2) No difference between the groups can any longer be demonstrated in the 2nd month of life; nor does any such difference appear later.

3) No difference can be demonstrated in the health of the infants in the different groups.

The author has also discussed the normal red-blood picture of the infant, and compared the result in this material with those from similar Swedish materials, investigated with much the same technique.

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## **Hyperchromic (pernicious?) Anaemia in Infancy.**

By

**F. KARLSTRÖM and G. NORDENSON.**

A case that very well illustrates the differential diagnostic difficulties in anaemia in children has recently been studied at the Karlstad Hospital.

The case was that of a boy, born on the 4th March, 1941. Nothing hereditary of interest in both father's and mothers family. The patient had 3 older brothers and sisters, who are all dead. The oldest died through an accident at the age of 19 months. The next oldest was stillborn. The youngest brother was born in proper time. After birth this brother often vomited and had attacks of diarrhoea, which grew worse from the age of six months. At the age of 15 months he was an in-patient of a cottage hospital. He had then been suffering from diarrhoea for 2 weeks. His weight was only 7 kilos. He died with the diagnosis acute gastroenteritis. No blood-test was made.

This boy was born at the proper time at his home and had a weight at birth of 5 kilos. Was given the breast until fully 12 months old. From the age of about 6 months mashed potatoes and very little other vegetables. Total quantity of milk hardly 1 liter per day. Appetite poor and occasional vomitings. From the age of about 6 months 2 teaspoonfulls of codliver oil per day. The increase in weight was good until the age of about 12 months and at the age of 7 months he weighed 8 700 grammes, at the age of 12 months 11 kilos.

At the age of about 12 months his appetite began to grow poor, he vomited more and his weight diminished, so that at the age of 18 months he weighed only 9.2 kilos. His psychic development was somewhat retarded. Control at a Children's Nursing Central where blood-tests according to Tallquist were carried out. These showed on the 27th November, 1941, 70 %, on the 12th

March, 1942, 70 %, and on the 29th April, 1942, 90 %. From the age of about 6 months the patient had been prescribed Liq. ferr. oxid. sacchar. at the rate of half a teaspoonfull three times daily, but this was only given sporadically. 2 weeks before the admission in the hospital he was regularly treated with Differosan and Aq. dest. aa half a teaspoonfull three times daily.

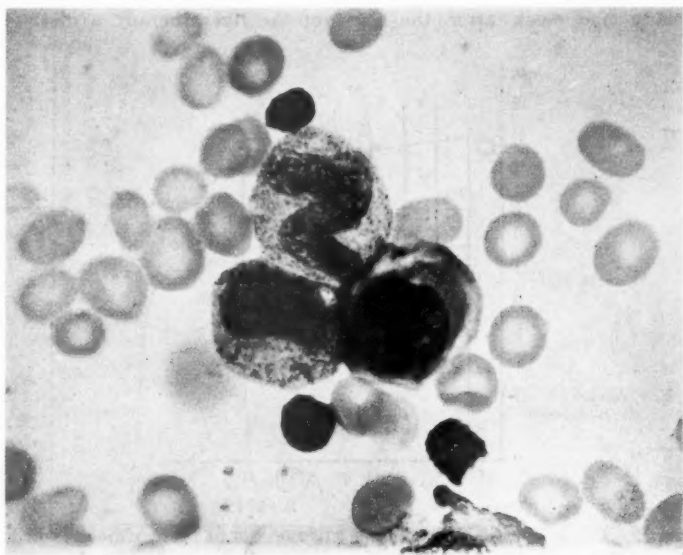


Fig. 1.

On the admission at the Central Hospital in Karlstad, on the 26th September, 1942, the patient was 18 months old. His weight was 9.2 kilos. He was very much emaciated, flabby of body and very pale. No rhagades round the mouth, the nails were not fragile. The tongue was strikingly smooth. He was whining and puling. No rachitic symptoms, 16 teeth. On both sides of the neck some glands of the size of a pea. The liver was palpated beneath the costal margin, the spleen was not palpable. At the heart a faintly systolic murmur was heard (which gradually disappeared during the stay at the hospital). W.R. was neg. in both the patient and his parents. The temperature varied during the first week at the hospital between 37 and 38°, with some peaks

up to  $39^{\circ}$ . Thereafter the temperature was perfectly normal. The urine did not display anything pathological. The stools were not particularly plentiful and of *normal appearance* and normal consistency. No diarrhoea. (No worm-eggs.)

During the first week at the hospital the patient's condition was still poorly. He lay inert, took very little interest in his surroundings, denied food and vomited several times daily. Already one week after the begin of the liver therapy a distinct

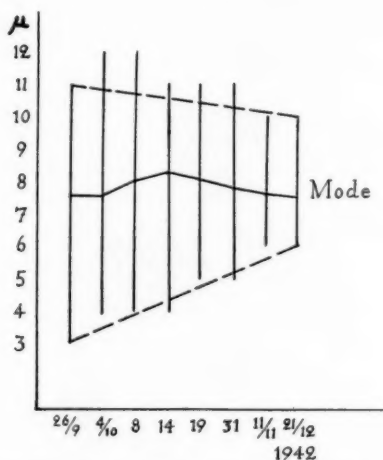


Fig. 2. Curve showing the variations in the size of the erythrocytes in  $\mu$ .

improvement was noticed. He grew livelier and more active, the appetite had improved and by and by he stopped vomiting. One month after the admission he was dressed, crept about on the floor and soon learnt to walk and speak a few odd words. His weight increased to start with very slowly but then more rapidly, and on being discharged from the hospital, on the 21st December, 1942, he weighed 11 kilos, and 3 weeks later 11.6 kilos. The weight curve was smooth and even without any pronounced peaks up or down.

After discharge from the hospital the patient pulled round excellently, had a good appetite, his weight increased and he was well and lively. Nearly all the time he was given Hepaforte  $\frac{1}{2}$  measure twice daily.

He was again an in-patient at the hospital between the 9th

November and 14th November, 1943. He looked then quite healthy, had a good colour, weighed 16.5 kilos, and his length was 93 centimeters, nothing remarkable from mucous membranes and internal organs. *Stools without remark (No worm-eggs).*

Serum iron (Dr. Bo Wahlquist) was on the 6th October and 25th October, 1942 respectively 115 and 110  $\gamma$  % approximately.

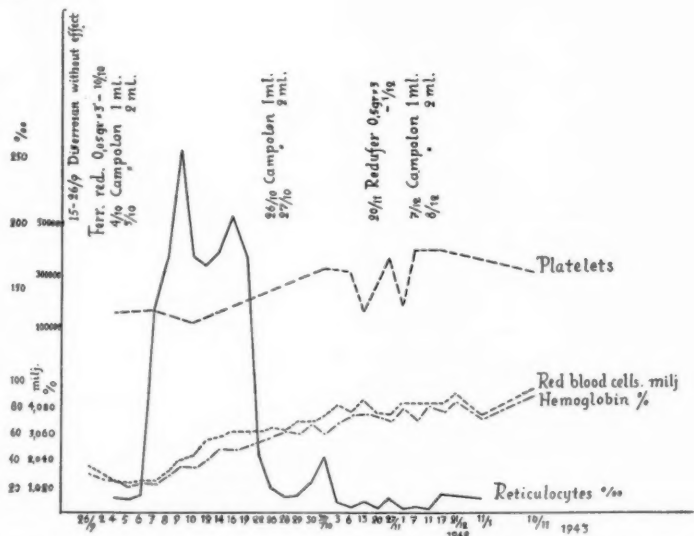


Fig. 3. Curve showing the variations in red blood cells, hemoglobin, reticulocytes and platelets.

The Meulengracht value was 1:4. Protrombin time normal.

Punctures of the bone marrow were made on the 28th September (see fig.), 10th October, 1942, and on the 9th November, 1943, with the following results.

28/9, 1942: Preparation rich in cells. In the myelopoiesis severe shift to the left with an increase of promyelocytes and myelocytes. Pronounced disturbance of the maturation process with considerable increase in the size of the cells. Nucleus loosened and displaying a bizarre shape and like a corkscrew, the form of a loop etc. These changes exist chiefly in metamyelocytes and rod forms. Mitoses to usual extent. Erythropoiesis



hyperplastic and dominant in certain spots of the preparation. Megaloblasts of various ages together with erythroblasts greatly preponderating, and normal normoblasts almost altogether lacking. Mitoses somewhat increased. Megacaryocytes rare. Reticulum strongly hyperplastic and all transitions to proerythroblasts present. (See fig. 1.)

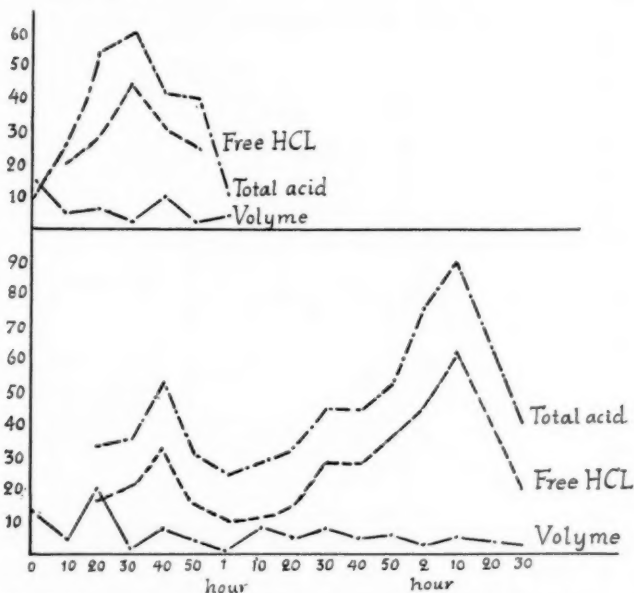


Fig. 4. Curve showing the results of two fractionated histamin tests.

*Diagnosis:* All criteria of a pernicious anaemia and the picture is identical with that we find with P. a. in adults.

10/10, 1942: Preparation with plenty of cells. In the myelopoiesis still shift to the left and disturbance of the maturation process. Erythropoiesis altogether changed. Megaloblasts practically altogether vanished. The picture is dominated by erythroblasts and normal normoblasts. Mitoses fairly numerous. Megacaryocytes rare. Reticulum slightly hyperplastic.

*Diagnosis:* Good remission of the pernicious anaemia.

Showing the alterations in the white blood cell picture.

White blood cells	26/9	4/10	8/10	14/10	19/10	31/10	6/11	1/12	16/12	21/12 1942	11/1	10/11 1943
	4 800	6 200	10 400	9 900	5 700	12 000	6 800	8 700	7 900	10 500	8 900	6 300
Myeloblasts . . . . .	—	1.0	—	—	—	—	—	—	—	—	—	—
Myelocytes . . . . .	0.5	—	1.0	—	—	—	—	—	—	—	—	—
Metamyelocytes . . . . .	—	—	—	0.5	—	—	—	—	—	—	—	—
Red forms . . . . .	3.5	—	—	1.5	1.5	3.0	—	1.0	2.5	1.0	1.5	5
Segmented . . . . .	4.0	8.5	5.0	13.0	8.5	28.0	21.0	77.0	49.5	34.0	27.5	38
Eosinophiles . . . . .	—	1.5	1.0	2.0	1.0	2.5	5.5	3.5	3.0	3.0	6.0	1
Basophilic . . . . .	—	—	—	—	—	—	—	2.5	1.0	—	1.0	—
Lymphocytes . . . . .	83.0	85.5	82.5	80.0	86.0	59.5	68.5	23.0	39.0	59.0	53.5	44
Monocytes . . . . .	7.5	2.5	5.5	3.0	1.5	6.0	5.0	3.0	5.0	3.0	10.5	12
Plasma cells . . . . .	1.5	1.0	—	—	1.5	1.0	—	—	—	—	—	—
Megaloblasts (per 200 white cells)	2	2	4	—	—	—	—	—	—	—	—	—
Normoblasts " " "	1	—	1	1	—	—	—	—	—	—	—	—
Basoph. stippl. . . . .	++	—	—	—	—	—	—	—	—	—	—	—
Polychromasia . . . . .	++	±	+++	±	±	±	—	—	—	—	—	—
Aniso-megaloeytosis . . . . .	++	++	++	++	+	±	—	—	—	—	—	—
Poikilocytosis . . . . .	++	++	++	++	±	—	—	—	—	—	—	—
Hypersegmentation in leucocytes	++	++	++	++	++	+	+	+	±	+	±	—

9/11, 1943: Preparation relatively poor in cells. In the myelopoiesis slight disturbance of the maturation process. Erythropoiesis without remark. Megacaryocytes rare. Reticulum somewhat hyperplastic — increase of monocytoid cells.

*Diagnosis: On the whole normal marrow.*

Blood tests: See tables and curves.

### Discussion and Comments.

Anaemia in infants and children is remarkably common. The most commonly occurring type is hypochromic with a low bloodindex, whereas the hyperchromic types are very rare, at least in our latitudes.

The symptomatic, hypochromic types of anaemia are due to disturbances of nutrition and infections of various kinds. The hyperchromic ones are partly constitutional but may have releasing moments in the form of infections etc. The hyperchromic types are often to be conceived as "primary" blood diseases, if by "primary" we mean a certain reaction of the erythropoieses. A classification from a purely morphological and also from a clinical point of view of the various types of anaemia is hardly possible, in as much as similar reactions may be released in the blood, depending upon the lability of the haemotopoietic organs in infancy. A typical example presents Jaksch-Hayem's anaemia, which formerly was considered as "primary" but is now conceived as symptomatic. In cases of grave symptomatic anaemia the extramedullary haematopoiesis in the liver and spleen may reappear, which makes itself manifest by a discharge of unripe cells in the circulation, when partly-coloured blood-pictures occur. With extramedullary blood-formation there occurs furthermore sometimes a tendency to hyperchromicity and macrocytosis. Purely leukemoid respectively "erythroblastosis-like" bloodpictures may also arise, which give an impression of malignant "blood-diseases", but where nevertheless the prognosis in many cases is good.

Characteristic may be the precens of erythroblastes, even proerythroblastes, which present great similarity with megalo-blastes. This cell constitutes the very youngest generation in

the erythropoiesis but does not occur after the 3rd foetal month. When now in view of the peripheral blood there are certain difficulties to distinguish the different types of anaemia, one may ask if not the change in the bone marrow might constitute a possibility of classification. Unfortunately, the intravital study of the bone marrow does not supply a safe basis for distinguishing "primary" and symptomatic erythroblastoses. On the other hand this method of examination might perhaps supply an exact diagnosis when it is a matter of real megaloblastic anaemia.

As a rule, it may be said that the symptomatic "erythroblastosis" rarely becomes as acute as the "primary" ones, which are also more malignant. The "primary" malignant types are, as has just been pointed out, rare — here may be mentioned Cooley's erythroblastosis, Sichelzellen-anaemia and Fanconi's anaemia. More common are haemolytic icterus and icterus neonatorum (with transition to Hydrops congenitus).

Actual megaloblastic blood formation displays *pernicious anaemia*, *Ziegenmilch anaemia*, anaemia in *sprue* and *coeliacia*, as well as certain *verminous affections*. Sprue-anaemia may nevertheless be of a hypochromic type, the same as anaemia in the case of verminous affection. It is, however, not sufficient for the erythropoiesis to be megaloblastic, but in the bone-marrow there must be the typical disturbance of maturation in the myelopoiesis, which makes itself manifest by hypersegmentation and increase in the size of the leukocytes. Characteristic is furthermore the enlargement of rod forms and metamyelocytes with a softening of the nucleus as well as the change of form of the nucleus into the most peculiar and bizarre nuclear pictures in the cells. All above-mentioned types of anaemia may display these criteria.

Ziegenmilch-anaemia may be excluded from the subsequent discussion, since it practically does not occur in our country. The child did not display any signs of verminous affection. There remains to discuss the possibility of pernicious anaemia or atypical sprue.

Many authors deny that a genuine pernicious anaemia on

the whole exists in children. Pernicious anaemia is a typical oldage disease, with a frequency maximum between the ages of 40 to 70 years (SCHAUMANN). Only few cases exist to be described below the age of 10. SCHULTEN considers that every such case should *a priori* be regarded with the utmost scepticism. But we believe that SCHULTEN goes too far when he formulates his conception in the following manner: "Die Diagnostik dieser Fälle wird sicher dadurch erschwert, dass die Kinderärzte keine Gelegenheit haben, klinische und hämatologische Erfahrungen über die Krankheit zu sammeln und daher leichter zu Fehldiagnosen auf diesem Gebiete neigen", which we interpret as a poor acknowledgement of the competency of pediatricians in haematological questions. The difficulty to differentiate the anaemias in infants we have, however, earlier pointed out. Some of the difficulties have, however, been eliminated through the intravital study of the bone-marrow, which is now carried out as a method of routine at every pediatric department of any size.

As regards the literature, NÄGELI has described 2 cases of pernicious anaemia at the ages of 8 and 11 years. No particular data of these cases could be obtained. DEBRÉ, MARIE, LAMY and LEDOUX-LEBARD, as well as ROTH and ISÉLI have published cases at ages respectively 6 and 4½ years. In both cases there existed normal secretion of hydrochloric acid in the ventricle. LICHTENSTEIN's case (Nordisk Lärbok in Pediatrik) may possibly be one of pernicious anaemia. The patient's age was 9 years. The youngest case hitherto described (9 months) has been published by DEDICHEN. On repeated occasions of examination the secretion of hydrochloric acid in the ventricle was absent. DEDICHEN seems nevertheless to a certain degree to doubt the diagnosis, in that he publishes the case as "anémie à type pernicieux".

The most important fact in the pathogenesis for genuine pernicious anaemia is the absence of the "intrinsic factor". In the pernicious-like sprue-anaemia this factor is, however, present in the gastric juice. Parallel with the loss of this factor runs achylia, which must be looked upon as being an

almost compulsory symptom in genuine pernicious anaemia. Achylia may in many cases have preceded the development of the anaemia. Achylia is due to an atrophy of the mucous membrane of the stomach, and this atrophy remains gastroscopically and roentgenologically also with complete remission of the anaemia. The question of the achylia, and thus the diagnosis, is, however, accentuated, since there are undoubtedly cases of pernicious anaemia which display free hydrochloric acid in the gastric juice after histamin stimulation. ALSTED has thus in the literature collected 32 cases of pure pernicious anaemia with retained hydrochloric acid secretion, and there exists thus an isolated disturbance in the production of the "intrinsic factor". The phenomenon is, however, so rare that in practice one need not take this into account. Scientifically, this must be regarded first and foremost in possible differential diagnostic.

Pernicious sprue-anaemia has as a rule a normal hydrochloric acid secretion. The occurrence of pernicious-like anaemia in sprue is considered to be due to a disturbance in resorption in the intestine, and thus a poorer exploitation of the "intrinsic factor". If possibly achylia or hypochylia were present the normal secretion of gastric juice is restored after healing. Even the atrophy of the mucous membrane of the ventricle disappears both roentgenologically and gastroscopically.

As regards the morphological-haematological picture, there exist certain differences between pernicious anaemia and sprue-anaemia. The index in the latter is often hypochromic. The index in this case is higher than the normal in children and the anaemia should therefore be designated hyperchromic (though the index only touched 1). Likewise leukopenia is less pronounced and instead we find leukocytes of a polynuclear type. Lymphocytosis is thus less common in pernicious-like cases of anaemia. In contradistinction to genuine pernicious anaemia there occurs often a manifest shift to the left in the white cell picture. In many cases of sprue one finds furthermore Jolly-bodies in the red corpuscles, which symptom is connected with the atrophy of the spleen that frequently oc-

curs in the sprue-syndrome. The reticulocytosis after liver-treatment displays the same characteristics in sprue-anaemia as in the genuine pernicious anaemia. The thrombocytes are less frequently affected in the pernicious-like anaemias.

In the punctate of the bone-marrow we find in both cases megaloblasts together with the almost specific disturbance in the maturation process of the myelopoiesis. Certain authors (SCHULTEN) consider themselves, however, to find a certain difference in the appearance of the bone-marrow. In sprue the megaloblastosis would be less pronounced, and the megaloblasts display certain morphologically different details. Furthermore, according to SCHULTEN one would also find more normoblasts than in the genuine pernicious anaemia.

From the discussion it is seen that we stop ultimately before a differential diagnosis between pernicious anaemia and an anaemia in atypical sprue. As regards the pernicious anaemia, one may perhaps say that theoretically such type of anaemia might very well occur in children, in spite of several authors denying the possibility. We have here a symptomatic picture which by no means points in any direction for a definite diagnosis. The picture resembles most the genuine pernicious anaemia, because perhaps the most important symptom of sprue is lacking — it would be so atypical that the abnormal pigmentation and the intestinal disturbance are lacking. In the pathogenesis for the two anaemias the relation of the anti-pernicious principle is of decisive importance. If one considers that "the intrinsic factor" belongs to the B-group of vitamins, and this opinion has many adherents, it is possible that this not easily interpreted case might belong to a more uncommon type of B-vitamin deficiency.

A definite diagnosis might perhaps theoretically be obtained by setting forth the liver-therapy when, if a genuine pernicious anaemia existed, a relapse sooner or later would make itself manifest. But this conflicts with the first principle of medical science: *salus aegroti suprema lex*.

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## **Meckel's Diverticulum and Intestinal Hemorrhages in Children.**

By

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Intestinal hemorrhages are very common in children and are usually due to banal causes which are not difficult to diagnosticate. But now and then there are cases where the cause or origin of the hemorrhage cannot be detected, in spite of the use of all the most modern diagnostic methods. During the last few years we have seen several such patients at the Pediatric Department of The State Hospital where it has not been possible to make an exact diagnosis. In studying the literature in order to gain some information, if possible, as to these unexplained cases, there was one condition which attracted attention, namely MECKEL's diverticulum and its pathological consequences.

MECKEL's diverticulum is said to be present in 1—4 % of all people. Further there may be intramesenterial diverticula from the small intestine. These are sac-like formations of varying size with their base on the mesenterial side of the intestine and lying between the two mesenterial folds, usually parallel to the intestinal lumen. These are very rare as only about 15 cases had been published up to 1938. Pathological conditions in such diverticula are relatively common. GREENWALD and STEINER report that among 81 cases of MECKEL's diverticulum found on post mortem examination (TURNER), there were pathological findings in 20, about 25 %. If these figures give a fairly accurate picture of the situation, it would be expected that about  $\frac{1}{3}$  % of all persons at one time or

another in their lives have a pathological condition in connection with MECKEL's diverticulum. But it is doubtful whether every pathologically altered diverticulum has given clinical symptoms.

This dangerous appendage is especially known for its tendency to cause ileus. Surgeons are also aware of the possibility of an infected or perforated diverticulum Meckeli in cases of indefinite, acute abdominal symptoms, and the diverticulum is always looked for and eventually examined in all cases of appendectomy where the condition of the appendix itself does not afford sufficient explanation of the symptoms. The severe hemorrhages which can be caused by peptic ulcers in the diverticulum are less well known.

The pathological conditions which may arise in connection with a MECKEL's diverticulum can be classified in 3 main groups:

1. Intestinal stenosis.
2. Diverticulitis.
3. Ulcus pepticum.

These complications have been observed in individuals of all ages but are more frequent in children. Most of the published cases have been in children under 1 year, usually boys. GREENWALD and STEINER have collected a material of 51 cases from the ages of 3 months to 1 year, of which 41 were boys. This same preponderance of boys has been found in most of the compilations made.

In connection with intestinal hemorrhage the last group, ulcus pepticum, is of particular interest. It is only in recent years that this condition has been generally recognized and studied, especially by American authors. In Norway cases have been reported by OTNES and LIAVAAG.

Pathogenetically ulcus pepticum Diverticuli Meckeli is closely related to ulcus ventriculi s. duodeni, as heterotopic stomach mucous membrane is often found in the diverticulum, as a rather large, continuous surface in the distal part of the diverticulum or as more isolated islands. It would seem

reasonable to assume that the ulcer arose someplace in this mucous membrane, and many authors have adopted this theory. But actually the ulcer is never found in the stomach mucous membrane, but on the contrary always outside these areas, in the intestinal mucous membrane, often just at the border of the stomach mucous membrane. It has been demonstrated that the heterotopic stomach mucous membrane both histologically and functionally is identical with the mucous membrane of the stomach proper. It secretes hydrochloric acid and pepsin, which have a destructive effect on the less resistant intestinal mucous membrane, giving rise to ulcerations in the same manner as an ulcer pepticum jejuni after gastroenterostomy.

The symptomatology is characterized chiefly by recurring hemorrhages. There are sudden, very abundant hemorrhages at intervals varying from weeks to several years when the patient is symptom free or has slight, indefinite abdominal symptoms. The blood may be bright red or dark and tar-like, often both types mixed. There is no hematemesis. The first hemorrhage usually occurs before the age of 2 years, seldom before 2 months. But one case has been described where the hemorrhages began 2 days after birth and recurred several times until the child was operated at the age of 5 months. The first hemorrhage may be fatal and every recurrence threatens the child's life. Severe anemia always develops subsequent to the acute hemorrhages, usually with a hemoglobin % of 30—40. The patient may also have numerous slight hemorrhages from childhood to maturity with no other consequences than a slight, secondary anemia. In some patients there are slight, more protracted hemorrhages. In the above mentioned series of 51 cases of MECKEL'S diverticulum 85 % had hemorrhages, and in many this was the only symptom.

There are sometimes severe colic pains, simultaneously with the hemorrhages or in the free intervals. They are usually localized to the navel region and have no relation to meals. The pains may be the first symptom and the hemorrhages

follow later. Vomiting is not rare, but no blood is vomited. Temporary fever has also been observed in some patients. Next to hemorrhages, perforation is the most frequent complication.

Palpation of the abdomen usually reveals normal findings when there is no perforation. Occasionally there is localized tenderness, especially in the navel region. When there is perforation the symptoms are the usual ones for an acute peritonitis due to perforation.

The diagnosis is difficult. The severe hemorrhages may lead to suspicion of a diverticulum when a careful examination affords no other explanation. Roentgen examination is usually of no help for the diagnosis. NOERMARK, who has described a case of intramesenterial diverticulum, points out that  $\frac{1}{4}$  of the cases of intramesenterial diverticula which he has collected, have been complicated with mediastinal cysts without subjective symptoms, and he therefore recommends roentgen examination of the thorax in all unexplained cases of melæna in children. The intramesenterial diverticula are not distinguished otherwise from MECKEL's diverticulum as far as the symptoms are concerned, and cannot be distinguished before operation. They are also most frequently found in children.

Other conditions which have differential diagnostic significance are ulcer duodeni, polyps of the large intestine, invagination, thrombosis of the splenic vein, purpura Hennoch, appendicitis. It should be mentioned that MECKEL's diverticulum may cause invagination, and in this manner lead to intestinal hemorrhage without any ulcer.

If the possibility of an ulcer diverticuli is born in mind, it should be possible to make at least a probable diagnosis. But it must be admitted that the diagnosis has been made in only a very few of the described cases before operation or post mortem examination.

The mortality from the diverticula of the small intestines giving manifest symptoms is very high, and without operation the prognosis is poor. Of the cases I have found published, about  $\frac{2}{3}$  ended fatally, the others being saved by operation.

It is obvious, however, that it is mostly the severe cases which have been published, and this may give an unnecessarily gloomy picture of the situation. The prospects of cure by operation are good if the child is in good health at the time of the operation. But as many are operated when in poor general condition as a result of the hemorrhages or other complications, the operation mortality is high; it is claimed to be 50 %. When there is justified suspicion of a diverticulum the patient should be operated during a free interval, if no ileus, perforation or other acute symptoms necessitate immediate operation.

On 7/9—43 was admitted to the Pediatric Department a new case of melæna, which may serve as an illustration of the above described condition.

This was a boy, b. 2/7—38. He was born at full term and had developed normally. Healthy until 3 1/2 years old. One day, in November 1941, he suddenly had thin, black fæces. The next couple of days very little, black fæces. He was hospitalized and his hemoglobin was 35 %. He underwent an ulcer cure for 4 weeks. The hemorrhages ceased very soon and he recovered rapidly. No explanation for the hemorrhages was found.

He was then in good health until April, 1943. At this time he had hemorrhages again, possibly more severe than the first, he was very pale and weak. He was again hospitalized and had a hæmoglobin % of 32. He was given blood transfusions and iron and underwent a new ulcer cure for 6 weeks.

After discharge he was not in good health. He often had acute abdominal pains, complained of nausea and vomited often, especially at night. He had still not recovered completely when he had his 3rd intestinal hemorrhage, this time less severe with hæmoglobin down to 65 %. He was again hospitalized for 14 days. After this his fæces were normal, never black, and he was comparatively well. As the mother was anxious for the child after the severe hemorrhages she consulted a pediatricist who sent him to the Pediatric Department.

On examination he was found to be a strong, 5 year old boy with a healthy appearance. Temp. 37.8. Cor, pulmones: Normal. Abdomen: Appearance normal. Soft, not tender. No palpable tumor except for the border of the liver which was palpable a fingers breadth below the costal arch. The testicles were not descended.

Laboratory investigations: Hb. 87 %. Red blood corp. 4.8 mill. Index: 0.9. White blood corp. 7800. Blood sedimentation 26 mm. Diff. count: Eosinophiles 2 %. Nonsegmented neutroph. 2 %. Segmented neutr. 62 %. Mono. 1 %. Lympho. 33 %. Thrombocytes 317000. Bleeding time  $3\frac{1}{2}$  min. Coagulation time 2 min. Prothrombin time 20 sec. Coagulum retraction good. Ewald ( $\frac{1}{2}$  hour): 125 cc., well digested. HCl/TA 26/52. Urine normal. Repeated examination of faeces: Benz.  $\div$ . Blood sedimentation rate fell in the course of a few days to 6 mm.

Roentgen examination: Stomach: Mucous membrane folds irregular, some secretion. Otherwise nothing to remark on the stomach or bulbus duodeni. R. Gastritis? Colon: Negative findings. Intestinal series: No definite pathological findings (rapid passage through the small intestines). Oesophagus: No indications of varices or other abnormalities. Pulmones: Negative findings.

In attempting to find the cause or origin of the hemorrhages after this case history we finally limited the possibilities to the following 4: Ulcus ventriculi s. duodeni, ulcus diverticuli Meckeli, polyps of the colon and thrombosis of the splenic vein. The boy had not exhibited any general tendency to hemorrhages, and it was most reasonable to assume that the hemorrhages must be due to a local process in the intestines. Nor did the blood analysis give any indications of a general tendency to hemorrhages.

The hemorrhages might well be due to an ulcer duodeni. In childhood this is manifest by severe hemorrhages, which may be the only symptom, while the symptomology is otherwise uncharacteristic. There was no roentgenological evidence in favor of this diagnosis.

The colon was examined particularly for polyps, but the roentgenologists found no indications of polyposis. Rectoscopic examination revealed no pathological findings. As far as I have been able to determine, it is unusual that polyps cause such severe hemorrhages as those of our patient. But even on the basis of the negative roentgen findings this diagnosis could not be excluded.

We believed that thrombosis of the splenic vein could be eliminated. The spleen was not palpable, he had never had hematemesis, and no oesophagus varices could be demonstrated

by x-ray examination. The palpable liver could not be ascribed any significance as it was probably not enlarged.

We thus came to the conclusion that ulcer diverticuli Meckeli was the most probable diagnosis. Roentgenologically no diverticulum was found, but a diverticulum can rarely be detected in this manner. A more exact diagnosis was impossible and after a conference with The Chirurgical Dept. A the patient was transferred for an explorative laparotomy on suspicion of MECKEL's diverticulum.

On 24/9—43 laparotomy was carried out in ether narcosis. Extirpatio diverticuli Meckeli (Dr. GADE). When the viscera pressed forth in the opening a large MECKEL's diverticulum was immediately noticed at the characteristic place on the ileum. The diverticulum was about 5 cm. long. There was a circular constriction about the middle, and distally to the constriction there was a plum sized swelling (Fig. 1). The diverticulum was extirpated by a wedge excision. Primary suture.

When the removed diverticulum was dissected (Fig. 2) it was found to consist of 2 distinct parts, a proximal part lined with ordinary intestinal mucous membrane with a Payerian plaque, and a distal part, the above described swelling, lined with mucous membrane which resembled that of the stomach. The border between these two types of membrane was sharp. No ulcer or scar after such was visible. Microscopy: In one part of the section there is intestinal mucous membrane with a sharp demarcation towards a mucous membrane which resembles that of the stomach with glands with goblet cells and parietal cells. The cells and nuclei are uniform in size and shape with no indications of atypia. In the stroma there is a diffuse infiltration of lymphocytes.

The patient reacted only slightly to the operation. On the 4th day he had 2 bloody stools and on the 5th day 1. He was given a blood transfusion on the 5th day. However the hemoglobin % was not lower than 72. Since that time there has been no indication of blood in the faeces. He recovered rapidly and was discharged symptom free.

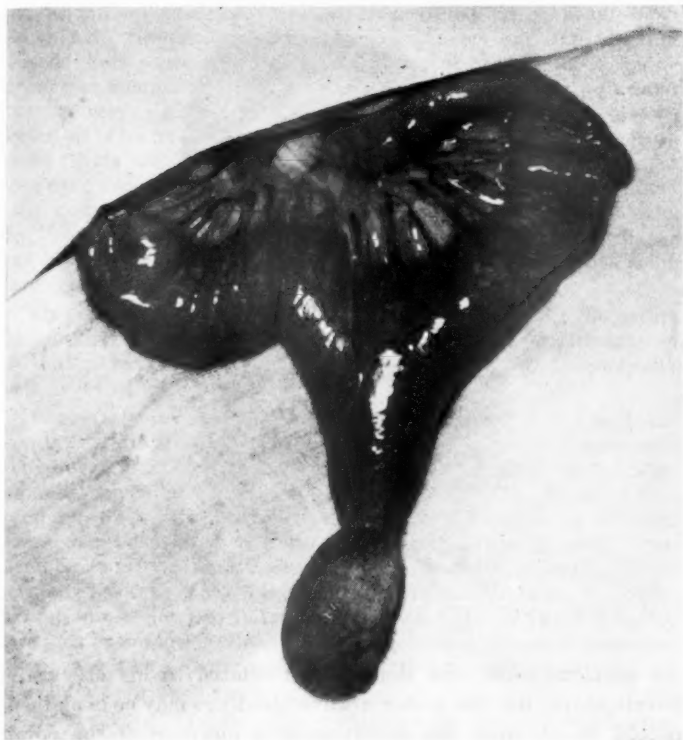


Fig. 1.

Now we are faced with the question: Were the intestinal hemorrhages due to his MECKEL'S diverticulum? As the diverticulum came into sight as soon as the abdomen was opened, we did not doubt the connection between the hemorrhages and the diverticulum. The case became more doubtful when no ulcer or scar was found. It is possible, however, that the hemorrhages are due to acute ulcers which healed without scars. The operation was performed  $2\frac{1}{2}$  months after the last hemorrhage. As for the hemorrhages after the operation, the objection may be made that these are of the same origin as





Fig. 2.

the previous ones, and thus neither related to his MECKEL's diverticulum. But the post-operative bleedings may be explained as old blood from the operation or a bleeding at the point of resection. In spite of these objections I believe that when we have a case history like the present which is best explained by a MECKEL's diverticulum, and when we find a diverticulum with abundant stomach mucous membrane which affords all the prerequisites for the development of peptic ulcers, and when we, as in the present patient have investigated all the other possibilities with negative results, we are justified in making the diagnosis: hemorrhages from ulcer pepticum diverticuli Meckeli.

Our next melæna patient supported this interpretation. This was a boy, b.  $^{29}/_1-42$ . Born at full term, breast fed for  $8\frac{1}{2}$  months. Previously healthy.  $^{19}/_1-43$  he had blackish-red fæces

and the 3 following days bloody fæces once daily, never fresh red blood. He was given an adrenalin enema and the bleeding ceased. For 8 days his fæces were normal but on the 9th day there was again dark red fæces. He was given barley water and then a very light diet. This was followed by a symptom free period of  $2\frac{1}{2}$  months. From  $14\frac{1}{4}$  to  $16\frac{1}{4}$  he had some fever, up to  $39.4$ . He also had a slight cold at this time. On  $16\frac{1}{4}$  he had abundant bloody fæces twice, once in the morning and once mixed with coagulated blood in the afternoon. He became very pale. On  $17\frac{1}{4}$ —43 he was admitted to the Pediatric Dept. A diaper was also sent containing abundant, blackish-red fæces with some dark, coagulated blood.

On examination the child was pale and irritable. No pathological findings on palpation of the abdomen nor on examination of the other organs. Temp.  $37.5$ . Exploration in the ampulla recti revealed bloody fæcalia.

Laboratory investigations: Hb. 56%. Red blood corp. 4 mill. Index: 0.7. White blood corp. 13000. Blood sedimentation rate 28 mm. Reticulocytes 21 ‰. Differential counts: Basophile  $1\frac{1}{2}$ %. Non-segment. neutr. 6.5%. Segmented neutr. 21.5%. Mono. 2.5%. Lympho. 69%. Thrombocytes 261000. Bleeding time 8 min. (subsequent control  $3\frac{1}{2}$  min.). Coagulation time 3 min. Prothrombin time 35 sec. Ascorbic acid in blood 0.80 mg%. Urine normal. Fæces: Benz. + momentarily, from  $24\frac{1}{4}$  benz. ÷. Sedimentation rate down to 12 mm on  $24\frac{1}{4}$ . Ewald: 40 cc. HCl/TA 14/30. Roentgen examination: Stomach: hypersecretion, otherwise negative. Colon: negative. Rectoscopy  $6\frac{1}{5}$ —43: Mucous membrane pale, no signs of ulcers or tumors.

He recovered rapidly after treatment by diet and administration of iron. Hb. on discharge  $7\frac{1}{5}$ : 76%. At this time the only diagnosis reached was the symptomatic diagnosis: melæna.

Because of the findings in the previously described patient the parents were requested to report at the department to control the child. A couple of days after this request was made, the child on  $30\frac{1}{10}$ —43 had an evacuation which consisted of red-brown blood. The following evacuations were not visibly bloody and the child did not become pale or weak. He was again admitted on  $30\frac{1}{10}$ —43. He was in good general condition. Ordinary clinical examination revealed nothing pathological. Rectoscopy: Normal. Hb. 91%. Red blood corp. 5.2 mill. White blood corp. 11200. Sedimentation rate 8 mm. Prothrombin time, bleeding time and coagulation time: normal. Roentgen: Stomach, colon, intestinal series: negative. Fæces: Benz. ÷ on repeated investiga-

tions. This time we felt confident suggesting laparotomy on suspicion of MECKEL's diverticulum.

On 15/11—43 laparotomy was performed in ether narcosis in the Chirurgical Dept. A: Extirpatio diverticuli Meckeli (GADE). After section in the midline the small intestine was drawn out and a typical MECKEL's diverticulum was found, coming off a broad base on the convex side of the intestine but bent up to the upper side of the mesentery of the small intestine to which it firmly adhered. The diverticulum was conical, about 4 cm. long and at its apex there was a hazelnut sized sac, demarcated from the diverticulum by a distinct constriction. The diverticulum was loosened and removed. The operation progressed without complications.

Dissection of the diverticulum revealed that it was lined with intestinal mucous membrane up to the constriction at the distal end. This distal sac was lined with a mucous membrane which macroscopically resembled that of the stomach. At the border between the 2 types there was a horizontally oriented 5 mm. long and 3 mm. broad sharply defined ulcer. The mucous membrane around the ulcer had slight radial folds. Microscopic examination: On the one side intestinal mucous membrane with lymph follicles, on the other side stomach mucous membrane with glands containing parietal cells. The epithelium is lacking in an area between the 2 membranes and here there are smooth muscles and connective tissue, with no reactive alterations. In the submucosa there is a slight infiltration of lymphocytes. No sign of specific inflammation or malignancy.

Post-operative development without complications and the child was discharged symptom free.

In this patient there can be no doubt that his ulcer was the cause of the hemorrhages. But in consideration of the small ulcer with only an epithelium defect and no reactive alterations, it is readily understood that such an ulcer may heal without leaving visible scars, especially as it lies at the border of the 2 kinds of membrane. This last patient was

operated just 3 weeks after the last hemorrhage and the ulcer was still open, while in the first patient, 2 1/2 months after the last hemorrhage, the ulcer had healed completely.

### Summary.

MECKEL's diverticulum is found in 1—4% of all persons and frequently gives rise to pathological conditions which may be classified in 3 groups: Intestinal stenosis, diverticulitis and ulcer pepticum. These complications are observed particularly in children, usually under 1 year of age. Ulcer pepticum develops due to heterotopic stomach mucous membrane in the diverticulum which secretes hydrochloric acid and pepsin causing ulceration of the intestinal mucous membrane. The symptomatology of these ulcers is characterized by severe, recurring hemorrhages. Other symptoms are colic, vomiting, fever. Perforation is frequent. High mortality. Treatment: operation.

Case histories: A 5 years old boy with 3 previous severe intestinal hemorrhages, admitted during a free interval. On operation a large MECKEL's diverticulum was found, the proximal half of which was lined with small intestinal mucous membrane, the distal half with stomach mucous membrane. No visible ulcer or scar. A 21 months old boy who had 2 severe and one slighter intestinal hemorrhage. On operation a short time after the last hemorrhage a small MECKEL's diverticulum was found with the same structure as the preceding one. At the transition between the intestinal and stomach mucous membrane there was a small ulcer.

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## **Ulcus pepticum in early childhood.**

By

**ERIK FRISELL.**

The occurrence of ulcus pepticum in childhood was observed at a comparatively late date. Not until the year 1862, when GUNZ described the first case of ulcus ventriculi in a child, was attention focussed on this phenomenon. During the course of the years, a number of compilations have been published illustrating the frequency of this disease in early childhood. With but a few exceptions, only autoptic material has been dealt with.

It will be seen from these cases that the frequency is greater during the first year of life than in the following years. Thus, SCHMIDT found 0.6 per cent ulcus duodeni (17 cases) among 2 705 post mortems on children of more than 1 year of age, while in 1 109 post mortems on children under 1 year of age the figure equalled 1.8 per cent (20 cases), i. e. in 3 out of 4 children with ulcus duodeni the age was below 1 year. The majority of the children in the latter group were in the age of 2—6 months.

In a material from three of the children's hospitals of Stockholm, BERGLUND found a corresponding figure for the first year of life of 1.10 per cent in 907 post mortems. When the cases with ulcus ventriculi were included in the calculation, the figure was 1.54 per cent. The first year of life predominated also here. In BERGLUND's total material, comprising children of up to 13 years of age, the ulcers constitute ulcus duod. in 14 cases, ulcus ventr. in 4 cases, and a combination of both in 1 case.

*The frequency of ulcer pepticum in infants in a few compilations of section material. (The figures in brackets denote the number of cases.)*

<i>Author</i>	<i>Num. autptic cases</i>	<i>Ulc. duod.</i>	<i>Ulc. ventr. + duod.</i>
BERGLUND . . . .	907	1.10 % (15)	1.54 % (19)
SCHMIDT . . . .	1 109	1.8 % (20)	
ENTZ . . . . .	364	2.7 % (10)	3.0 % (11)

According to the compilations from the literature, neither sex discloses any definite prediposition. Nevertheless, some authors believe they have detected a greater frequency among boys.

No hereditary factors have emerged. Still, ulcer duod. was once found in two infants of the same family (ROGERS).

While a true ulcer pepticum is, invariably, a primary occurrence in adults, the ulcer is always secondary in infants. Infancy forms a period of transition in so far as the ulcers at this age are, occasionally, primary. Basing his investigations on material hitherto published, FINKELSTEIN arrived at the conception that every case of ulcer pepticum is secondary before the age of 5. Other authors have tried to prove the opposite. Thus, for instance, GUTHRIE declared, without drawing any definite conclusions, that he had been unable to find any ascertainable cause in 7 cases out of 9 with ulcer duod., 8 of which were under 1 year of age.

These infantile ulcers may appear in connection with acute or chronic infections, metabolic disturbances (uremia and nephritis, oxidations, eczema, and cachetic conditions), as well as traumata and circulation disturbances. In particular, atrophic children of all ages appear to be predisposed to these ulcers. In up towards 50 per cent of the cases, in several of the materials of earlier authors, the diagnosis of pedatrophia was present. 11 of BERGLUND'S 19 fore-mentioned cases, among children up to 13 years of age, revealed a bad state of nutrition, while 5 were normal, and 3 very good.

One mortal instance of *ulcus acutum duodeni* was noted at the Sachs Children's Hospital which appears to be of some interest. The child was 13 months old at admission.

D. R., a girl, 13 months old, was admitted in February, 1943. (Record number 131/43.) The youngest of two children, of healthy parentage. Both parents under the age of 30. No mental diseases in the family. Spontaneous delivery 14 days too soon, no complications. Weight at birth 2850 g. Breast fed till almost 1 year old. Control examination at the Bureau of Children's Welfare. Prescribed Cod Liver Oil. B. C. G.-vaccination when 6 months old. At first, unsatisfactory increase in weight. She was backward and, for instance, never learnt to sit steadily, nor had she grown any teeth. A doctor at the Children's Welfare Bureau had informed the mother that the girl had a Mongolian appearance and prescribed Tabl. Thyreototal mite, 1 tabl. twice daily.

The child had always suffered from sluggish evacuation, earlier with only 1 evacuation a week, and after thyreototal medication, usually once a day.

Three days prior to admission, the child was uneasy during the whole day, but otherwise as usual. (The mother had diarrhoea.) In the next morning, the child became very pale and apathetic, slept almost the entire day and refused food. As the mother thought the child was sick owing to the sluggish bowels, she gave it  $\frac{1}{2}$  a tablet of a laxative (Purex).

On the day before admission, a loose, comparatively abundant excretion in the morning, partly mixed with light blood, otherwise a brown colour. Still equally pale and apathetic, whimpering and uneasy as on the day before. Fell asleep in the afternoon, but again became uneasy in the evening, screamy, and lay tossing. This kept on through the night. On one occasion, a small vomiting fit with a dark stomach contents of approximately 1 dessertspoonful mixed with blood. On the following morning, before leaving for the hospital, the child had an abundant loose, brown evacuation with light lumps.

State at admission: General condition strongly affected, somnolent, reacting but slightly to external stimulation. Distinct Mongolian appearance. The skin had a corpse-like pallor with yellow patches. Pale, dry lips with small coatings of dark, coagulated blood. Lowered tonus and turgor.

The heart: a faint systolic blur over the apex. The abdomen: soft, appeared somewhat large. Palpation gave no reaction on the part of the child. Skeleton: the skull without remark, the

rosary slightly above normal, no teeth. Reflexes: patellar-pos. bilat., pupils reacted faintly to light.

Röntgen (abdominal survey): No free liquid or gas ascertainable in the abdomen (JONSELL).

The child was transferred to the Surgical Department of Kronprinsessan Lovisa's Vårdanstalt (Record number 264/43) for surgical consultation.

Abdomen: completely soft all over.

Blood: Hb 17 %. Red bl. corpuscles 920 000, white bl. corpuscles 11 400. Diff.: myelocytes 1 %, rod-nuclear leukocytes 20 %, segment-nuclear leukocytes 37 %, lymphocytes 29 %, monocytes 13 %. Thrombocytes 45 000. Nucleus carrying red bl. corp. 6/100 c. white. Pronounced anisocytosis. Prothrombin time (acc. FIECHTER): 15 sec.

Urine: 0.

The child's conditions deteriorated rapidly. After about an hour she was dead.

Post mortem: Ordinary build of the body. Wax pale, with edema in the hands, legs and feet. Bilat. epicanthus, snout-shaped nose, clumsy hands and feet. Heart: medium position, no malformations, pale myocardium. Thoracic cavity and lungs: 0. Abdominal cavity, thyreoidea, thymus: 0. Oesophagus: a lump of tar-coloured mucus in the inferior part. Ventricle: tar-coloured mucus and a coagulum the size of a nut in the canal part, continuing into the duodenum. The bulb wide and containing a longitudinal coagulum, in all the size of a nut. The posterior wall stained intensely red, but lustrous (taken for micr. exam.). Pink femoral medulla.

Microscopic examination (FALCONER).

Duodenum: the mucous membrane is lacking in the macroscopically stained region, thus leaving the deeply located glands bare. The edges of the defect are badly stainable. Also, a slight leukocytic infiltration is noted.

*Diagnosis:* Ulcus acutum duodeni.

Bone medulla: Reveals no deviation from the normal.

The clinical diagnosis of ulcer pepticum in infants has almost invariably been determined accidentally, generally, when several cases of this kind have accumulated and attention has been on the alert. The course is either acute, with marked hematemesis or melena and death within a short time, or the ulcer has a more chronic development and the symptoms become more diffuse, viz., vomiting and, possibly, only microscopical



blood admixtures in the faeces. A great number of the cases refer to the first days of life and are classified under the definition *melen a neonatorum*.

A number of cases clearly establish a connection between pylorospasm and ulcer. The diagnosis is, however, complicated by the fact that the admixture of blood to the vomiting is no unusual occurrence in pylorospasm alone. The question of which of the two diseases is the primary one is, as yet, unsolved. Thus, it has been impossible to determine whether an ulcer can stimulate to spasms in the pylorus ring, or is due to a nutrition disturbance caused by the state of cramp, or to the continuous vomiting fits.

Hemorrhages from the intestine are of differential-diagnostic interest in polypus and intussusception, hemorrhagic diathesis and profuse bleedings in connection with infections (capillary lesion).

The prognosis is extremely unhelpful. Nevertheless, there have been instances of spontaneous healing.

Blood transfusion plays a prominent part in the treatment, which is otherwise pronouncedly conservative. Surgical intervention is indicated only when perforation is definitely established.

In the majority of cases, the duodenal ulcers are located to *pars horisontalis duodeni*, just below the pylorus, generally on the dorsal side. Thus, in BERGLUND's material, the ulcers were located within a distance of 1 cm from the pylorus ring. On the other hand, the ventricular ulcers seem liable to appear anywhere in the mucous membrane of the ventricle. One or several ulcers may occur in both these localizations.

Opinions differ considerably as regards the mechanism of origin of *ulcus pepticum* in childhood. Nor is, in fact, the origin very likely to be uniform. The theory of a spasmogeneous ulcer is believed to apply to adults rather than to children. Another theory propounds that a state of deteriorated nutrition together with a functional injury to the epithelium of the mucous membrane should form a prerequisite for the appearance of thrombosis of the mucous membrane with ensuing

secondary changes. As regards ulcer in infectious diseases, the possibility of bacterial toxins causing increased production of hydrochloric acid by reflective means has been conceived.

According to yet another theory, the predisposed factor (i. e. the infection) should occasion an altered reaction position with a change in the vessels produced by allergic means. The connection between ulcer pepticum in early infancy and pylorospasm has been briefly discussed in the preceding.

Etiological factors, with the exception of Mongolism, are lacking in the case described in the present paper. In earlier compilations, BURDICK, among others, mentioned a case of ulcer duodeni in a Mongolian boy who died before the age of 3 months. Since Mongolism is characterized by, inter alia, a series of degenerate phenomena of the body, it is possible that the intestinal ulcer may, also in this connection, be a secondary occurrence owing to a general degeneration of the physical constitution.

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## **Zerebrales arteriovenöses Aneurysma bei einem kleinen Kinde.**

von

**JUSTUS STRÖM.**

Die zerebralen arteriovenösen Aneurysmen zählen zu den kongenitalen Missbildungen (TÖNNIS). Daher ist es um so bemerkenswerter, dass wir in der Pädiatrie so selten derartige Fälle sehen. Diese Aneurysmen sind indes vielleicht nicht so selten in den Kinderjahren, wie wir bisher vermutet haben. Manche Fälle von subarachnoidalen Blutungen bei Kindern entpuppen sich vielleicht allmählich derart, dass man die Ursache in Aneurysma verschiedener Natur sehen muss. Ich weise hier auf den ganz kürzlich in dieser Zeitschrift (Bd 31) erschienenen Artikel von ÅKERRÉN hin.

Wie dem auch sei, sind die zerebralen arteriovenösen Aneurysmen mit dem für Erwachsene typischen Krankheitsbilde im Kindesalter ausserordentlich selten. So hebt TÖNNIS in BERGSTRAND-OLIVECRONA-TÖNNIS-Monographie »Gefässmissbildungen und Gefässgeschwülste des Gehirns« hervor, dass sich in 7 von den 22 Fällen von OLIVECRONA und TÖNNIS die ersten Symptome im zweiten, in 7 Fällen im dritten, in 3 Fällen im vierten, in 4 Fällen im fünften und in 1 Falle erst im sechsten Lebensjahrzehnt gezeigt haben. Dieses Verhalten erklärt TÖNNIS dadurch, dass die auftretenden Symptome durch lokale Veränderungen im Gehirn verursacht sind, die sich ziemlich langsam entwickeln, als eine Folge von verschlechterten Zirkulations- und Ernährungsverhältnissen in der Umgebung des Angioms. Abgesehen von Fällen, die mit Symptomen subarachnoidaler Blutungen anfangen (z.B. einer von den Fällen

von TÖNNIS und ÅKERÉNS Fall) beruhen die ersten Krankheitszeichen also auf den folgenden Gehirnveränderungen. Gewöhnlich bestehen diese Symptome in epileptischen Anfällen von Jackson-Typ.

Man kann also beim Auftreten von einseitigen motorischen oder sensiblen *Jacksonanfällen* eine Wahrscheinlichkeitsdiagnose auf Grosshirnaneurysmen stellen. Diese Anfälle sind von meistens vorübergehenden motorischen oder sensiblen Störungen begleitet. Kommt hierzu eine *Subarachnoidalblutung*, kann man mit grosser Wahrscheinlichkeit darauf schliessen, dass es sich um ein zerebrales Aneurysma handelt. Ausserdem können gewisse, sehr langsam zunehmende motorische und sensible Symptome vorkommen. Dagegen sind chronische Hirndrucksteigerungen und Stauungspapillen selten. Von den Augen können vereinzelte Male andere Symptome auftreten, wie abnorm verschlungene Gefässe im Augenhintergrund und unscharf begrenzte Papillen. In vielen Fällen ist ein gleichseitiger, nicht pulsierender Exophthalmus konstatiert worden.

Zwei Symptome ermöglichen nach TÖNNIS die Sicherstellung der Diagnose: durch Röntgen nachgewiesener, typischer kreisförmiger *Kalkschatten* und systolisches *blasendes Geräusch* über dem Kranium. Erstgenannter lag in 3 von den 22 Fällen von TÖNNIS-OLIVERCRONA vor. Blasendes Geräusch fanden CUSHING-BAILEY nach TÖNNIS in 8 Fällen von 9, aber T-O nur in 4 von 22 Fällen. Wichtig ist, sich dieses Symptoms zu erinnern, das nicht so selten zur richtigen Diagnose führen kann. So verhielt es sich in meinem Fall.

In anderen Fällen muss die Diagnose mit Hilfe von röntgenographischen Untersuchungsmethoden gestellt werden. Das *Enzephalogramm* zeigt eine leichte Verschiebung nach der gesunden Seite, und dieses soll selten fehlen. Die wichtigste Untersuchung ist die *Arteriographie*, wodurch nicht nur die Diagnose Aneurysma gestellt werden kann, sondern auch ein klareres anatomisches Bild erhältlich ist, das für die Beurteilung der operativen Möglichkeiten von Bedeutung ist.

Nach diesem kurzgefassten Überblick über Pathogenese, Symptomatologie und Diagnostik bei zerebralem arteriovenö-

sem Aneurysma gehe ich dazu über, über einen Fall zu berichten, den ich 3 Jahre lang in meiner Privatpraxis beobachtet habe. Dieser hat sein spezielles Interesse, da die Symptome schon im 4. Lebensjahre angefangen hatten, und die Diagnose auf rein klinische Symptome hin schon früher hatte gestellt werden können als in irgend einem, bisher bekannten Fall.

*Krankengeschichte:* Am 11.5.1937 geb. ♀. Geb.-Gew. 4 000. Körperliche Entwicklung normal. Psychisch ihrem Alter voraus. Ich habe sie im Laufe dieser Jahre viele Male gesehen. Ihr Aussehen war immer bemerkenswert. Der Kopf ist immer gross gewesen (im Alter von 2½ Jahren 53 cm, mit 4 Jahren 55 cm). Das Gesicht oval mit ungewöhnlich hoher Stirn und grossen Augen. An den Schläfen und in den Augenlidern haben immer zahlreiche Blutgefässe durch die dünne Haut geschienen.

Pat. hatte von Geburt an im Capillitium einen kleinen Tumor, der im Alter von 2 Jahren extirpiert wurde. Es handelte sich um eine Hämangiom.

Das Mädchen entwickelte sich gut und erst kurz vor Eintritt in das 5. Lebensjahr ereignete sich etwas Bemerkenswertes. Eine Nacht erbrach das Kind mehrere Male. Zwei Tage danach schien sie verwirrt zu sein, begriff nicht, was gesagt wurde und sprach eigentümlich. Sie verdrehte Worte und Begriffe, sagte z.B. »streiche Butter auf mich« und dergl. Gleichzeitig hiermit begann sie zu schielen.

10 Tage danach, am 8.5.1941, wurde ich konsultiert und konnte dabei nur konstatieren, dass sie einen deutlichen Strabismus hatte, der nicht beständig war, aber oft hervortrat, indem das linke Auge meistens nach aussen abwich. Die Beweglichkeit der Augen war übrigens o.B. Die Pupillen reagierten normal. Vom Nervensystem sonst nichts Bemerkenswertes.

Ich konsultierte einen hirnchirurgischen Spezialisten (Dr. SJÖQVIST), der dasselbe fand wie ich. Auch der Augenhintergrund wurde beiderseitig untersucht und wies nichts Abnormes auf. S. war der Ansicht, dass eine zerebrale Anomalie im Gefässsystem vorliege. Weitere Massnahmen sollten indes nicht ergriffen werden.

Acht Monate danach wurde ich von neuem zurategezogen. Das Mädchen erbrach nun mit 1-2-3wöchigem Zwischenraum des Morgens, bei jeder Gelegenheit mehrere Male. Sie erwachte, sah sehr bleich aus; es war ihr schlecht, und sie erbrach einige Male mit Schleim vermisches Wasser. Dann ging es vorüber, und tagsüber war nichts zu merken. Sie wies denselben Strabismus auf wie früher und eine gewisse Konvergenzinsuffizienz (15—20 cm).

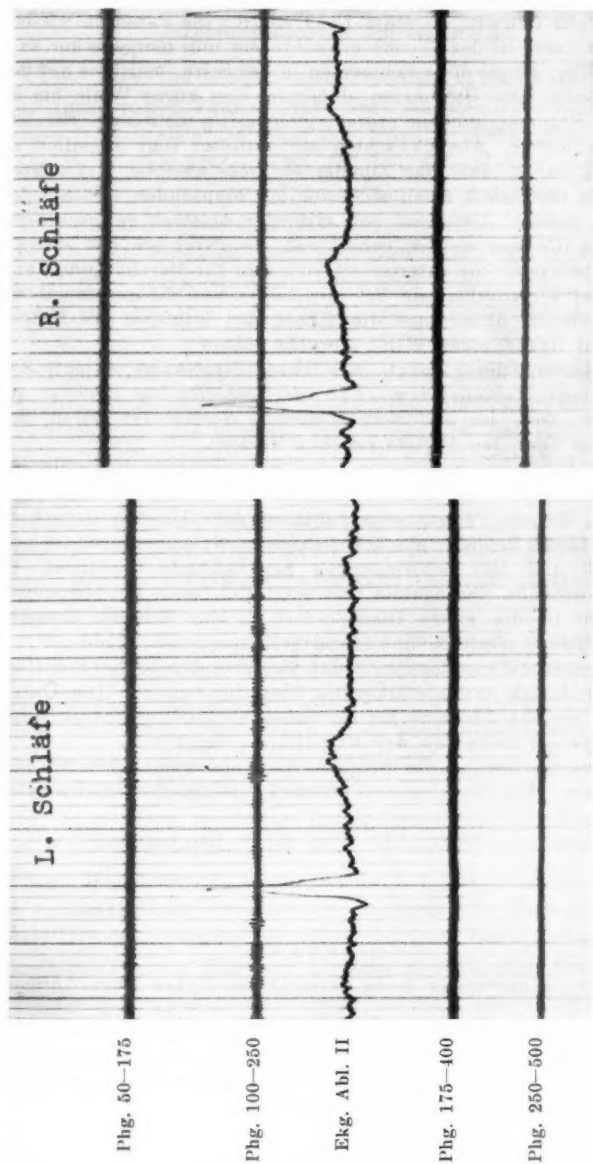


Abb. 1. Elektrokardiogramm (Ekg) in Ableitung II und Phonogramm (Phg), über den Schläfen aufgenommen, im Frequenzgebiet 50—500 Schwingungen per Sekunde.

Ein Jahr danach, im März 1943, sah ich die Patientin wieder. Ungefähr 1mal in der Woche erwachte sie nun morgens um  $1\frac{1}{2}$  6 —  $1\frac{1}{2}$  7 Uhr, klagte über Schmerzen in der Stirn, meistens auf der linken Seite. Die Schmerzen dauerten eine kurze Weile bis zu ein paar Stunden, und sie erbrach gleichzeitig mehrmals. Strabismus wie bisher. Abends schien sie mitunter sehr ängstlich zu sein und sagte, dass das Zimmer so gross aussehe. Im letzten Jahre hat man auch einen eigentümlich brausenden Laut an den Schläfen gehört. Der Laut soll mitunter so stark gewesen sein, dass man ihn von weitem gehört hat. — Psychisch hat sie sich rasch entwickelt. Sie interessiert sich sehr für Märchen und kann sie gut wiedererzählen, sie hat alle Zahlen und die meisten Buchstaben gelernt, ohne dass die Eltern das Interesse des Kindes hierfür in irgend einer Weise geweckt hätten.

Die Untersuchung zeigte wie früher Strabismus. Nichts Abnormes vom Nervensystem. Über den Schläfen, am stärksten auf der linken Seite, ist ein stark brausendes Geräusch zu hören, das allmählich über den Parietalknochen vertönt.

Es schien mir von Wert zu sein, eine objektive Registrierung dieses Geräusches zu erhalten, weshalb ich Dr. MANNHEIMER hinzuzog, der ein Phonogramm aufnahm (Abb. 1). Sein Gutachten lautet: »Linke Schläfe: ein hochfrequentes Nebengeräusch ist zwischen 50 und 500 Schwingungen per Sekunde registriert. Es beginnt nahe an der Systole und setzt sich ohne nennenswertes Crescendo in die ganze Diastole fort. Rechte Schläfe: dasselbe Nebengeräusch, obgleich mit etwas geringerer Amplitude.

*Nebengeräusche vom kontinuierlichen Typ* über den beiden Schläfen, über der linken etwas stärker als über der rechten. Die Untersuchung spricht für eine arteriovenöse Verbindung intrakranial, wahrscheinlich links von der Mittellinie gelegen.»

Röntgenuntersuchung des Schädels ist 2mal ausgeführt worden, zuletzt am 12.3.1943, wobei nichts Pathologisches nachweisbar war.

Augenstatus im März 1944: (Dr. K. O. GRANSTRÖM).

$$\begin{array}{l} \diagup r = \\ S \\ \diagdown l = 0,6 \text{ a } 0,8 \end{array}$$

Periodische Konvergenz recht beträchtlich, linkes Auge. Augenbewegungen o.B. Pupillen o.B. Skiaskopie:  $r. + 3,0$   
 $l. + 3,5$

Die Medien klar. Beiderseitiger Augenhintergrund o.B. (Papillen unbedeutend verwischt begrenzt, jedoch völlig physiologisch).

Diagnose: Strab. conc. conv. period. sin.

### Zusammenfassung und Erörterung.

Pat. hatte ein kongenitales Hämangiom im Capillitium, das im Alter von 2 Jahren exstirpiert wurde. Ausserdem wurde schon früh beobachtet, dass der Kopf ziemlich gross war, und dass an den Schläfen und in den Augenlidern ein abnorm reiches Gefässnetz vorlag. Im Alter von 4 Jahren bekam das Kind einen zerebralen Insult mit Erbrechen, temporärer Benommenheit, Sprachstörung und Strabismus von nicht beständigem Typ. Der Strabismus bestand weiter, und es zeigte sich, dass die Pat. eine Hyperopie hatte, sonst aber nichts Pathologisches von den Augen. Hiernach begann Erbrechen zentraler Natur, das allmählich den Typ linksseitiger Migräne annahm. Gleichzeitig mit diesen Symptomen kam ein brausendes Geräusch vom Schädel zum Vorschein, das sich auskultatorisch und phonographisch als ein kontinuierliches blasendes Geräusch erwies. Das Phonogramm zeigte, dass das blasende Geräusch nahe an der Systole beginnt und sich über die ganze Diastole erstreckt. Der Laut ist auf der linken Seite am stärksten. Röntgenaufnahme des Schädels hat ein negatives Resultat ergeben.

Was die *Diagnose* betrifft, ist diese nach dem Auftreten des kontinuierlichen blasenden Geräusches über dem Schädel sichergestellt. Es liegt ein arterio-venöses Aneurysma vor, das nach dem auskultatorischen und phonographischen Befund hauptsächlich links von der Mittellinie belegen ist.

Das *Krankheitsbild* bekommt hierdurch seine natürliche Erklärung. Der zerebrale Insult muss höchstwahrscheinlich auf einer subarachnoidalen Blutung beruht haben. Das linksseitige Migränesyndrom steht offenbar mit der Horizontallage in Zusammenhang (möglicherweise durch eine Blutansammlung und Drucksteigerung bei einer solchen Lage bedingt). Der Strabismus muss dagegen als eine unabhängige Erscheinung betrachtet werden, ein gewöhnlicher periodischer konvergenter Strabismus im Zusammenhang mit Hyperopie. Der zerebrale Insult hat hier doch wohl als ein auslösendes Moment gedient, vielleicht dadurch, dass die zentrale Fusion gestört worden ist.



*Die Therapie* des zerebralen arteriovenösen Aneurysmas ist gewöhnlich nicht erfolgreich. Nur wenige Fälle eignen sich für eine operative Therapie. Unterbindung zuführender Arterien lässt sich schwierig ausführen, da gewöhnlich mehrere vorkommen. Extirpation ist nur einige wenige Male gelungen.

Tiefbestrahlung mit Röntgen soll eine günstige Wirkung haben können.

Da im hier vorliegenden Falle die schweren Symptome fehlen, vor allem Jacksonsche Anfälle, die im allgemeinen für diese Aneurysmen kennzeichnend sind, dürfte eine radikalere Therapie bei den mit einer solchen verbundenen Gefahren ausgeschlossen sein. Wenn in Zukunft epileptische Anfälle hinzukommen sollten, muss man natürlich eine Operation in Erwägung ziehen. Für die Patientin hat es sich darum gehandelt, die migräneartigen Anfälle zu mildern zu versuchen, was auch durch Behandlung mit Phenemal in kleinen Dosen ziemlich gut gelungen ist.

Die Prognose ist natürlich dubiös. Subarachnoidalblutung ist immer eine Gefahr. Die Patientin hat, wie erwähnt, wahrscheinlich schon eine solche gehabt, und man muss darauf vorbereitet sein, dass ein solches Ereignis wieder eintreffen kann.

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Vol. XXXII. Fasc. 2

15: I. 1945

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*Almqvist & Wiksells Boktryckeri Aktiebolag*  
UPPSALA 1945

# ACTA PÆDIATRICA

EDITOR PROFESSOR I. JUNDELL  
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## **Incorrect diagnosis of mental deficiency and its consequences.<sup>1</sup>**

By

**ANNA-LISA ANNELL, Lic. Med.**

It not infrequently happens that children are admitted to our institutes for the mentally deficient under a diagnosis of feeble-mindedness, and then later on show favourable development. These cases can be divided into two fairly well-defined groups, the first consisting of children between the ages of 9 and 11 years who are capable of learning, and the second of infants who are remitted to mental institutes before the age of 1 year as hopeless imbeciles. In the first group, in addition to children suffering from psychosis or severe forms of psychopathic disease, we may place those with aphasia, dyslexia, or pure environmental disorders. The general tendency among physicians and schoolteachers seems to be to designate all children unable to keep up with the school work as imbeciles. Actually, the fact that these children are classified incorrectly is in many cases of little practical significance, since the general lack of auxiliary classes or of special classes for these categories in Sweden makes the placing of them in special schools for defectives the only possible solution of the problem for the present.

In the case of the other group, on the other hand, comprising young infants diagnosed as hopeless idiots, the consequences are more serious, not only for the child itself —

<sup>1</sup> From a lecture delivered at a meeting of the Section of Pediatrics and School Hygiene of the Swedish Medical Association, October 13, 1944.



although it does not as a rule suffer any deleterious effects from spending a few years at an institution during the pre-school period — but more especially for the mother, in whom the thought of having a permanently defective child often affects the psychic balance, which in its turn redounds upon the harmony of the family life.

I have therefore included in the appended case reports a description not only of the condition of the child, but also, when the circumstances were known, of the reaction of the mother and the effect upon the family in general from having a child of this type in their midst.

### Case reports.

*Case 1.* J. O. K., male, born July 11, 1943.

Treated at a children's hospital from July 31 to Aug. 17, 1943. Diagnosed by a physician as a mongolian idiot. Hospital diagnosis: Mongolism.

The patient's mother was extremely nervous and emotional, suffering from occasional anxiety attacks. His maternal grandfather and great grandfather had been alcoholics. He was an only child, born six weeks before term. Birth weight: 2,670 Gm.

Physical condition on July 31 (at 20 days old): Mottled skin. Horizontal eye-slits. A large protruding tongue. Normal tone and turgor. The anterior fontanelle measured a fingertip in width, and the sutures of the skull were normal. The root of the nose was broad and flat. He had a frog belly and a diastasis recti abdominis. He sucked the breast with normal vigour.

Epicrisis on Aug. 17: Signs of mongolism observed when the patient was admitted. The typical mongoloid features had become more marked as time progressed, and the diagnosis was therefore considered established. Because of the depressed condition of the mother, however, the mental state of the child was not revealed to her. Nor was anything said to the father, who was doing his military service.

The patient was re-admitted on Sept. 7, 1944, at the age of 14 months, because he was difficult to bring up and was sleeping badly. He showed normal development in all essentials. He could stand and walk a little, but was irritable, cried a lot, and always wanted someone near him.

Physical condition on Sept. 7: His general condition was good. He was plump, with normal musculature. The root of the nose

was unusually flat. Epicanthus was present but the eyes were not slanting. The fingers were short and clubbed. He had six teeth, stood, played, and said a few disconnected words. I. Q. = 116 (by the Bühler Hetzer method).

*Case 2. B. E. A., female, born on Apr. 9, 1943.*

Treated at a children's hospital from Feb. 10 to Feb. 15, 1944. Diagnosed by a physician as a case of mongolism. Hospital diagnosis: Mongolism.

Family and personal history: The mother had always been very nervous. The father was diabetic. The patient was the first and only child. The mother was 45, the father 42 years old at the time of the patient's birth. The child had grasped at objects from the age of 7 months, and could stand with some assistance from 9½ months. She could babble but no words were distinguishable. She was a docile and placid child.

Physical condition on Feb. 10 (at 10 months old): A well developed girl baby showing the signs typical of mongolism. The skull was rounded, the hair abundant and fairly coarse, the face round, with red cheeks. The eyes were slanting in an upward and outward direction, the corners of the mouth pointed downward. She had a saddle nose and there were signs of epicanthus. She seemed to have convergent strabismus. The folds of the ears were slightly asymmetrical. The tongue was normal. She had no teeth. The anterior fontanelle measured a fingertip in width. The skull was firm, the skin not especially dry. Moderate muscular hypotonia. It was possible to attract her attention, she grasped at objects, could sit unaided, and stand if supported. The Wassermann reaction was negative. She was discharged and sent straight to a home for the mentally deficient.

From this institution the following report was received. On admission, the patient seemed somewhat flaccid, and was fairly difficult to feed, but her body and joints were not so lax as the bodies of mongoloid idiots generally are. At the end of one week she was livelier, ate well, gained in weight, sat up, played, took an interest in her surroundings, and began to say a few words. At the age of 11 months she could crawl and stand unaided. The development was completely normal. The mother visited the child while she was at the home. She had been told by the physician who sent the child to the hospital that her child was mentally defective, and she had been so upset that she had had a nervous breakdown and had therefore never come to see the child in the hospital. She had typical mongol features, with slanting eyes, dark streaky hair, and outstanding cheekbones.

She stated that she had Mongolian blood in her veins, her paternal grandfather having been a Russian and of the Mongolian race. The child was thus a Mongol. She was removed from the mental home at the end of 3 months and has apparently continued to develop normally.

The mother's condition, on the other hand, is not satisfactory. She is more nervous than before, she is under the care of a psychiatrist, and is abnormally suspicious of both her husband and the physician, believing that they design to injure or do away with her child.

*Case 3. T. G., male, born on Nov. 18, 1941.*

Treated at a children's hospital in February 1942.

Family and personal history: Nothing of interest in the family history. The patient was the third child, the other children were normal. He was one of twins. Birth weight: 3,300 Gm. His twin sister weighed 3,800 Gm. at birth. The birth was normal. He had a large head from birth. Occasionally cyanotic. He cried a lot and slept poorly. At the age of 2  $\frac{1}{2}$  months he began to have convulsive attacks, these taking the form of tonic cramp over the whole body followed by intense fatigue. He had four attacks during 3 days, and was then sent to hospital.

Physical condition on Feb. 2, 1942: A hydrocephaloid child, with a large skull and a pear-shaped head. Circumference of head, 47 cm. (circumference of chest, 40.5 cm.). Graefe's test was not definitely positive. The measurements of the anterior fontanelle were  $6 \times 6$  cm., and there was slightly increased tension. There was a diastasis 1 cm. in width between the parietal bones. The posterior fontanelle measured a little more than a fingertip in width. The skull was firm. It was possible to attract his attention, he could balance his head, but did not grasp at objects.

Encephalographic examination: The septum pellucidum and the third ventricle were in the median plane. The right ventricle measured 2.5 cm. across and the left ventricle 2.3 cm. On the whole, they were symmetrical, moderately distended, and rounded in outline. The third ventricle was abnormally wide, the transverse measurement being almost 1 cm. No air on the convexity. Diagnosis: Internal hydrocephalus.

The parents were informed that the prognosis was bad, and at the age of 6 months the patient was admitted to a home for mental defectives. While he was there he was completely lax and apathetic, and was difficult to feed on account of his flaccidity. At 7 months he had varicella. At 9 months he became

ill from an acute infection, probably pneumonia, his temperature being  $39^{\circ}$ — $40^{\circ}$  C. for a week. During this period he was very ill, and the lower part of his body was edematous. At the end of a week there was a critical drop in temperature, and at the same time a noticeable and rapid somatic improvement. A couple of days later he became brighter mentally, he could focus his eyes, watched the movements going on around him, sat up after one week, began to play, babble, tried to stand, and could walk with a little help at the age of  $10\frac{1}{2}$  months. He was discharged at 11 months old, when he appeared to be completely normal. The circumference of his head had decreased 2 cm. Since then he has developed normally, and if anything, he is slightly ahead of his twin sister as far as development goes.

*Case 4.* G. Ö., female, born Nov. 11, 1937.

Treated at a children's hospital during the period Apr. 26—May 8, 1938. Diagnosis: Microcephalia (porencephalia), congenital nystagmus, and convergent strabismus.

The birth was normal. The patient was the first child.

Physical condition on Apr. 26, 1938: The cranium appeared to be abnormally small, measuring 38 cm. in circumference (circumference of chest, 43 cm.). The anterior fontanelle measured  $1.5 \times 1.5$  cm. Convergent strabismus. Rhythmical nystagmus, most pronounced in the left eye. Patellar reflexes noticeably exaggerated. Nothing abnormal about the other reflexes.

Encephalographic examination: Distended cavities on the convex surface. No other features of interest.

Epicrisis at the hospital: A 5 months old baby which focussed the eyes, attempted to grasp objects, and made babbling sounds. The patient had marked microencephalia, congenital nystagmus, and heightened patellar reflexes, and the encephalogram revealed distention of the cavities on the convex surface. Because of these features it was assumed that the child in all probability would be feeble-minded, and partly to prevent the mother, who was unmarried, from becoming too attached to the child it was sent to a home for mental defectives.

At the home to which the child was admitted, at the age of 6 months, she showed rapid development, walked at an early stage, displayed surprisingly good muscular activity, and at the age of  $1\frac{1}{2}$  years did rhythmical dancing at a party at the home. She learned to talk at the normal time, played, and was lively and healthy. In 1940 she was examined by a children's psychiatrist in Stockholm and was certified as being mentally normal. This caused certain difficulties. The child's mother, who had lost

all contact with her child, did not want to have anything to do with her, and the Child Welfare authorities were annoyed at having been given incorrect information regarding the child's mental prospects. The problem of what to do with her was solved, however, by a nurse at the home taking her as a foster child. She has continued to show satisfactory intellectual development but she displays a number of psychopathic features. She concentrates with difficulty, and is abnormally lively and temperamental. She still has the nystagmus and consequently has some difficulty in doing her schoolwork. She does well in practical subjects.

*Case 5. V. S., female, born June 21, 1934.*

An application for admission was made to a mental home when the child was 6 months old. The certificate, which had been issued by a medical practitioner who was not a specialist, contained little information regarding the child, except that she was a typical mongoloid idiot. She was first admitted when she was nearly 2 years old. At that time there were no somatic signs of mongolism, but the patient appeared to be apathetic and backward. When she was about 2  $\frac{1}{2}$ , she became livelier, began to take an interest in her surroundings, was quick to learn, but had an uncertain temper. There is no further information regarding her development until 1940, when it was decided to discharge her from the home as she was obviously not mentally defective.

Some time after this decision the child's maternal grandmother approached the Inspector of Mental Homes with the request that the physician who had sent the child to the home as well as the physicians and directress of the institution should be held responsible for the damage they had caused through incorrect treatment. According to her statements, the mother's life had been ruined and the child deprived of a home and a harmonious upbringing. When the patient was born the mother was living with the patient's father, and it was their intention to marry. When the mother learned that the child was defective, she fell into despair, was terrified of becoming pregnant again, and would not allow the man to approach her. This caused a break between them. This break, and the sorrow over the child had had such an effect on the mother that she became ill with a psychosis some months later and had to be sent to a mental hospital. Since then she has never been completely well. She has several times been discharged from the hospital on trial but she has not regained her mental balance. There was thus no home for the child to return to, her grandmother was too old to take charge of her, and at the time when the grandmother

first made her application the patient had already been taken as a foster child by two families in succession. The grandmother therefore requested to be informed how physicians can be permitted to make such mistakes.

The patient's continued development has not been entirely favourable. She is in an auxiliary class at school. She is fairly gifted, but is suffering from a rather serious form of psychopathia and is temperamental and troublesome, and it has therefore proved difficult to find foster parents who are willing to keep her for any length of time.

*Case 6.* G. W., male, born in 1930. Details as to date are lacking.

The father, a County Council official, approached me in 1942 for advice with regard to his wife. She had always been sensitive and slightly nervous. They had married fairly young and after some years a boy had been born. The mother was then about 30 years old. They had taken the boy to a doctor because he was not eating well, and had been told that he was a mongoloid imbecile. A specialist in Stockholm whom they consulted had confirmed the diagnosis and advised them to send the child to a home for mentally defective children. He was admitted at the age of 7—8 months. The mother was completely broken up, was depressed, could find no joy in life, was afraid of having any more children and refused to have any further sexual intercourse with her husband. This had caused quarrels, and after some 5 or 6 years they had decided to separate. At about this time the father visited the patient at the mental home — acting on the physician's advice they had not been to see him after his admission, in order to spare the mother's nerves. He found a fairly normal boy and was informed that the child's development had been quite normal from the age of about 2 years. The child was taken home, and they renounced the idea of a divorce. When I saw the boy he was 12 years old. He showed no signs of mongolism, and was in the second class at a secondary school, where he was doing quite well. The mother, on the other hand, has not recovered. Her nerves are still bad, she is anxious and depressed, is completely »dead» sexually, and displays exaggerated solicitude for the boy.

*Case 7.* G. F., male, born Aug. 31, 1932.

One of the father's brothers is a schizophreniac, and a sister of the mother's has suffered from transient attacks of psychosis. The father has Finnish blood in his veins, several of his brothers

and sisters have epicanthus. The father is a priest. Two older children in the patient's family are normal. The patient was delivered normally, but at the time of his birth it was observed that he was malformed, had a fairly severe umbilical hernia, and syndactylism of the hands and feet. He is also said to have presented the typical mongoloid characteristics, with slanting eyes, epicanthus, a broad root to the nose, and a tongue protruding between the lips. He was operated upon immediately for the rupture. At the age of 11 months he underwent an operation to correct the syndactylia of the hands. The physical examination showed a normally plump boy, with normal tonus and turgor. The appearance of the face was slightly mongoloid, the eyes were slanting and fairly wide apart, the bridge of the nose broad. He had convergent strabismus and epicanthus. There was syndactylism of the hands and feet, the fourth and fifth fingers being joined in the hands and the second, third, and fourth toes in the feet. As regards the fingers, the terminal phalanges were more intimately united, there being only a shallow furrow between them, while there was a good fold of skin between the proximal phalanges. The operation was successful.

The child developed comparatively slowly during the first year. He could not focus at 6 months, but it was difficult to pass judgment on this point owing to the patient's strabismus. He learned to walk fairly late, but he could talk at the normal time. As time went on, his muscular development proved to be poor, his walking was awkward, he often stumbled, was slow in doing up buttons, and so on. Otherwise there were no abnormal signs. He now goes to school and is in the fifth class at a primary school, and next spring he is to try for admission to a secondary school. He is short-sighted, wears glasses, and is still clumsy in his movements, but there is otherwise nothing abnormal about him.

For the mother, the diagnosis made at the patient's birth was a great shock. She was deeply affected and concentrated all her attention on the defective child, completely neglecting both her husband and the two older children, as well as her parish work. Abandoning her previously well balanced religious views she began to go to extremes, one year taking up with the Pentecostal Movement, the next with the Oxford Movement. She was intensely afraid of having any more children. After about a year, the patient's two elder brothers began to be nervous, restless, and destructive, and had periods of defiance. The mother then went to pieces completely, was convinced that all her children were mentally deficient, and broke off all sexual relations with



her husband. When the patient was 3  $\frac{1}{2}$  years old, she consulted an ophthalmologist about his strabismus and was informed that there was nothing wrong with the boy except for his somatic symptoms. This relieved the nervous tension so completely for the mother that she regained her calm, began to take an interest in her other children and her husband, resumed a normal sexual life, and at the end of about a year gave birth to another child which was normal in every respect.

It is clear from the evidence of these cases that a faulty diagnosis and incorrect estimation of the prognosis with regard to young children with mental defects is a not uncommon occurrence. For the children themselves, a mistake of this kind does not have such serious consequences, but for the mother the shock can cause severe psychic damage which sometimes continues even after it has become evident that the child is showing normal mental development. In almost every instance these errors are made at an early stage, before the child has reached the age of one year. An incorrect diagnosis is seldom made after the age of one or two years.

We must therefore ask ourselves whether there is no possibility of improving our diagnostic methods, and if not, whether it is necessary to make the diagnosis so early.

The cases of feeble-mindedness diagnosed as such at the infant age are those displaying malformation, birth injuries, and mongolism. When serious malformation is present there is little risk that an incorrect diagnosis will be made, but if this should happen it has little practical significance since these children, even if they develop normally from the mental point of view — and this does occur occasionally —, never become capable of looking after themselves, and special arrangements of one form or another have to be made for their care all through their lives. Patients with birth injuries are more difficult to judge, but the chances of diagnosing incorrectly are not very great if the child really presents signs of psychic defect, because babies with injuries sustained at birth show a gradually deteriorating development; in other words, the feeble-mindedness becomes more and more evident, the children stand still or even become worse mentally, and ac-



tual dementia with permanent loss of what they have already learnt is a not unusual occurrence.

Mongolism, on the other hand, is worthy of special attention. It is a common form of mental deficiency occurring all over the world, among all races — the Mongol race not excluded — and in all classes of society; if any difference at all is distinguishable then it is that it occurs with greater frequency among the upper classes. Mongolism is diagnosed in a great many cases while the children are still in their infancy. According to TREDGOLD, mongolism constitutes 40—50 per cent of the forms of idiocy diagnosed in children under the age of one year.

The diagnosing of mongolism is generally considered to be easy. In the current textbooks on pediatrics the syndrome is described as absolutely characteristic — for the purpose of differential diagnosis only certain forms of myxedema and chondrodystrophy can come into question —, and the prognosis is said to be entirely unequivocal, the patients who survive being without exception mentally backward to a high degree. Most physicians also judge their cases according to these principles. If they encounter a child having the typical mongoloid appearance they see no reason for hesitating either in the matter of the diagnosis or in pronouncing the prognosis hopeless.

It might therefore be of value to bear in mind the statements made by HOMBURGER at the conclusion of his chapter on mongolism. He wrote as follows: »Zum Schlusse möchte ich noch einen mir wichtig erscheinenden Punkt erwähnen: es gibt eine nicht unbeträchtliche Zahl von Kindern ... welche zwar nicht das vollausgebildete Syndrom des Mongolismus zeigen, aber doch eine Mehrzahl seiner Symptome, so die Mongolenfalte und die Knopfnase, die Falte und den krummen kleinen Finger, die Lidspaltenbildung und -stellung mit schuppender Haut bei rundem Kopf. Darunter sind leicht schwachsinnige, aber auch durchschnittlich befähigte, sicher nicht schwachsinnige Kinder. Sie haben nicht den blöden Ausdruck aber doch ein befremdendes, in der Richtung der mongolischen

Rasse abweichendes Aussehen. Man gewinnt den Eindruck, als nähme sowohl die vollausgebildete mongoloide Idiotie als die »Formes frustes» des Mongolismus mit leichter geistiger Schwäche und lebhaftem Wesen, als schliesslich seine leichtesten die Psyche noch nicht berührenden ersten Andeutungen an Häufigkeit zu.»

The fact that patients are encountered with features resembling those of mongolism but with no psychic defects has also been mentioned by other authors. In 1937, WILHELM MALZ published a report on 30 patients who displayed various characteristics typical of mongolism, such as epicanthus, slanting eyes, macroglossia, and hypotonia, but who nevertheless had normal mental capacity, and from these observations he came to the conclusion that there must be latent forms of mongolism. Among other cases, he had one in which changes in the second phalanx of the little finger were established by radiography. This point should be stressed, because some physicians consider that such a finding confirms a diagnosis of »true» mongolism. ROSENBERG maintained as long ago as 1924 that the marked decrease in the number of mongolian children of a somewhat higher age might depend partly on the high mortality among infant mongols, and partly on the fact that in the milder cases both the somatic and the psychic symptoms often gradually recede, and sometimes disappear entirely.

In patients with genuine mongolism the prognosis is not so unequivocal as many physicians have hitherto believed. Although mongolism is in many cases allied to idiocy this can hardly be said to be the rule. In children who survive, the mongolism usually takes the following course: During the first year of life the child as a rule is flaccid and apathetic and its development in general slow. About the time when the child learns to walk, this being as a rule somewhat delayed, in other words at 1 1/2—2 years of age, there occurs a change, in that it becomes livelier, it walks and runs about, is curious and meddlesome, docile and playful, but a little defiant and disobedient. The child retains this more erethitic nature for

the rest of its life. A real development takes place from this time onwards, but it is slower and more incomplete than in normal children. The child usually develops until it reaches the borderline between imbeciles who are capable of learning and those who are not, and after that it comes to a standstill. There is often reason to try them out in schools for mental defectives, where they learn to read and write disconnected words. They are poor in arithmetic but musical, and they enjoy listening to singing and playing. They make no progress in theoretical subjects, however, and they are therefore generally transferred to classes for practical subjects where they often do well at work of a more mechanical type such as weaving. Most of them, however, have to remain at mental institutions.

One feature which I have not seen mentioned in the literature but which, judging from my own observations and from the statements of experienced members of the staffs of mental homes, would seem to be correct, is that the capacity of mongoloids for learning and for any further psychic development often comes to an end when they reach the age of 11—12 years. They have great difficulty in assimilating any fresh impressions after this age. The investigations carried out by BENDA in America, from which he demonstrated that mongoloids cease to grow in height at an early age and that they rarely grow any further after the age of 15, would seem to provide evidence in support of my observation. If their capacity for bodily growth ceases at this age it seems not unlikely that their mental development is also suspended earlier than in normal persons.

An investigation published in 1942 by POTOTZKY and GRIGG proved that, in the mongoloids in their series who reached the age of 16 years or more, the mean mental age was 6 years and 10 months, and that their social age was higher than their mental age. A number of the girls made good house cleaners and some of the boys became gardeners. These investigators also maintained that a few of these patients are intelligent enough to be placed in auxiliary classes or have

a mental status bordering on the normal. They considered, therefore, that the term mongolian idiocy should be entirely abandoned and mongolism used instead.

Although the prognosis in mongolism is more hopeful than has hitherto been supposed, it is important that physicians should be able to distinguish between genuine mongolism and cases of apparent mongolism. Apart from the typical mongoloid appearance of the patients, the presence of different features has been stressed by different authors as being essential, or a reliable assistance, for avoiding an incorrect diagnosis. One author mentions hypotonia, another the changes in the bones, in particular hypoplasia of the second phalanx of the little finger, a third the thick »wrestler's neck», a fourth the presence of any kind of malformation. None of these signs is reliable. It would seem to be essential, on the other hand, that the patient should display genuine mental defects in addition to the somatic abnormalities. If an infant looks like a mongoloid but is bright and lively and not at all backward or only slightly delayed in its development, then the diagnosis is uncertain. The typical characteristic is that mongolian children are flaccid and apathetic during the first year of life. It should also be borne in mind that the signs show a general tendency to improve, and this apparently continues until the patient is about 11—12 years of age. Thus, when there is no noticeable mental deficiency, extreme caution should be exercised in making a diagnosis, and it is preferable that the child should be kept under observation rather than that the mother should be informed at once of the diagnosis.

As has already been mentioned, in my experience an incorrect diagnosis is very seldom made in children over the age of one year, but in infants below this age it often occurs. The question arises therefore whether the diagnosis must necessarily be made at such an early stage, and whether it would not be sufficient to keep these children under observation for a time. The reason why it has been considered best to diagnose the condition as early as possible is that, by doing so, the child can be separated from the mother before she has

had time to grow fond of it. This mitigates the shock of parting, and in addition there is less risk that the mother will refuse to hand the child over to the care of an institution at a later stage. It is thought that, if she is separated from her child, the mother will be more likely to want another one. If there are other children in the family it is considered to be a wise measure to remove the defective child from the mother's care so that she will not be tempted to concentrate her attention on it to the exclusion of the other children.

In my opinion, it is doubtful whether these difficulties are most satisfactorily overcome by separating the mother from the child at an early stage. The reaction of the mother observed in almost every instance, that of fear and distaste at the thought of having any more children, seems to last as long whether the mother keeps the child or hands it over to an institution. It is a feeling of anxiety which goes deeper than the layers of the purely mental processes; it reacts upon her attitude to her husband, throws her sexual life into disorder, and cannot be dispelled by mere reasoning. The only way to relieve it would seem to be to endeavour to soften the shock experienced when she is told that her child is feeble-minded and that she must be parted from it. It is undoubtedly right that the child should be taken away from the mother, both for the child's own sake, in order that what possibilities for mental progress it possesses may be encouraged, and for the mother's; and when there are other normal children in the family it is absolutely essential. But from what I have been able to observe, there is no risk in delaying for a time before taking the step. The mother will then have time to get used to the idea and there will be more opportunity to make sure of the diagnosis. It is my belief that during the first months there is an intimate biological attachment between mother and child, a continuation of the biological process which began for the mother when she became pregnant, and that this lasts approximately for the period corresponding to the normal suckling time. To separate the mother and child during this period is therefore a serious intervention. In some

cases it has been found easier to do it when the child is 9—12 months old. If one waits until this time there is a likelihood that the diagnosis can be definitely established. Furthermore, before they reach this age, many of these children die, and the mother can then be spared the knowledge, and the shock this implies, that she has given birth to a defective child.

*Summing up*, it may be said that too little attention seems to have been paid hitherto to the conditions in infants which resemble mongolism but are not allied to mental defects, and which to a large extent disappear as the child grows older. In uncertain cases, therefore, the final diagnosis should be delayed until the child has reached the age of about one year, after which age an incorrect diagnosis is not often made. Another point to be stressed is that the prognosis in genuine mongolism is not entirely hopeless and that a certain amount of development, admittedly somewhat limited, is often possible. Sureness in the matter of the diagnosis and the prognosis is of paramount importance not the least for the sake of the mothers of these children. It is seldom possible to make any positive contribution to the treatment of a mentally defective child. The best thing we can do is to concentrate on the mother, and through her on the family in general, with a view to mitigating the effects of the presence of a defective child on the normal members of the family.

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## Some new clinical Observations on Hydrops congenitus.

By

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The following case of *Hydrops universalis congenitus* is of interest as it contributes to the elucidation of some new aspects of the clinical picture of this condition.

*Mother* aged 24. Primipara. Healthy during pregnancy. Wa. R.—. Delivery normal.

*The child* born  $15/4$ , 1944 exhibited extensive general edema at birth. Weight at birth 2250 g. Length 42 cm.

The child was admitted to the department  $17/4$  on account of the edema. It exhibited general, extensive, severe edema, deep marks remained everywhere after finger pressure. Ascites and hydrothorax could not be definitely demonstrated. Weight 2110 g. Slight icteric yellow color of the skin. The child had a hypothermia of  $35.6^{\circ}\text{C}$ . but otherwise its general condition was good. Heart and lungs normal. The edema of the abdominal wall made it impossible to investigate the size of the liver and spleen. The urine was normal.

The child thrived relatively well. Temperature became normal after a couple of days. The edema improved rapidly and by  $24/4$  had disappeared completely. At the same time the child lost weight steadily and on  $24/4$  was 1780 g. Gained weight slowly from this date. The liver and spleen were at that time not palpable. The icterus was of a medium grade and had disappeared  $20/4$ .

Discharged  $3/5$ . A control examination of the child on  $19/5$  revealed nothing pathological.

The blood investigations are presented in the following table:

	17/4	18/4	19/4	20/4	21/4	22/4	23/4	24/4	25/4	3/5	10/5
Hemoglobin % . . . . .	140	140	140	132	133	135	135	135	136	125	112
Erythrocytes mill. . . . .	6,8	6,5	6,0	6,0	6,0	6,0	6,0	6,2	6,2	5,3	5,0
Reticulocytes % . . . . .			47	35		20		2	2	1	1
Nucleated bl. corp. . . . .	37 000	25 000	15 000	11 000	11 000	11 000		12 000	10 000	12 000	10 000
Erythroblasts, % of the nucleated . .	32	28	11	4,8	0,39						
Erythroblasts, % of the red corp. . .	1,7	1,1	0,3	0,1	0,02						
Erythroblasts, total count . . . . .	11 658	7 015	1 607	714	109	0	0	0	0	0	0
White blood corp. . . . .	25 300	18 000	13 400	14 300	10 900	11 000		12 000	10 000	12 000	10 000
Myeloblasts and myelocytes % . . .	1		0	0	0	0		0	0	0	0
Metamyelocytes . . . . .	5		1	2	0	0		0	0	0	0
N. band forms . . . . .	15		23	19	7	4		8	2	8	0
N. polynucleated . . . . .	30		36	33	28	24		21	24	10	24
Eosinophiles . . . . .	0		6	3	5	4		6	3	0	5
Basophiles . . . . .	0		0	0	0	0		0	0	0	0
Lymphocytes . . . . .	46		32	35	57	65		61	66	77	68
Monocytes . . . . .	3		2	2	3	3		4	5	5	3
Blood sedimentation mm. 1 hour . .	1				1					1	2
Albumin in blood serum % . . . . .			3,00					3,62		3,72	
Globulin . . . . .			0,91					1,29		1,73	
Total protein . . . . .			3,91					4,82		5,45	
Oncotic pressure cm. H <sub>2</sub> O . . . . .			22,7					27,6		29,7	
Rest N mg. % . . . . .			11,7					15,2		18,7	



This is a case of a child born prematurely with general edema and whose blood (on the 3rd day) shows a marked erythroblastosis. The condition can hardly be interpreted otherwise than as a case of *Hydrops nniversalis congenitus cum erythroblastosis foetalis*.

The case illustrates the following features of interest:

**Hydrops congenitus is not an absolutely lethal affection.**

Hydrops congenitus has hitherto been regarded as implying stillbirth or death at the latest within the course of the second day after birth. The patient described here shows, in spite of its premature birth and severe edema, a relatively good vitality. The edema began to improve on the 3rd or 4th day after birth and had disappeared completely by the 8th day. During this period there was a loss of weight of about 500 g. from 2250 at birth to 1780 on the 9th day. From then on the child gained normally and thrived. A control examination when the child was 5 weeksold revealed nothing pathological.

The author has previously (6) described 2 cases of erythroblastosis foetalis which survived. These exhibited neither edema, icterus nor anemia. Even though no edema could be clinically demonstrated, one of these 2 children showed such marked disconcordance between weight at birth (3720 g) and length (47 cm), that it was reasonable to assume that the child suffered from latent edema. A certain general bloatedness of the skin also pointed in this direction. The other child showed no such disconcordance between weight (3580 g) and length (51 cm).

These cases are probably only variations in degree of one and the same condition. In its most extreme forms it results in intrauterine death and the delivery of macerated, hydropic embryos. From these extreme cases there are all transitional stages with delivery of live, hydropic children who die immediately after birth, hydropic children who survive when the edema disappears, and finally children who are born with erythroblastosis alone and only slight or no edema.

### **Hypoproteinemia as the cause of the edema?**

The pathogenesis of the edema in hydrops congenitus has been the object of much speculation. Nephritis in the mother, undernourishment (lack of vitamins) during pregnancy, increased capillary permeability in the child, various hormonal disturbances et al. have been discussed. One of the most obvious possibilities: a reduction of the albumin content of the blood and a consequent reduced colloid osmotic pressure in the blood, does not seem to have been touched upon.

In our patient there was a marked reduction of the plasma proteins. At the same time as the edema disappeared there was a sharp rise, especially of the albumins necessary for maintaining the osmotic pressure in the blood (see table). This brought about a considerable rise in the colloid osmotic pressure of the blood, from 22,7 cm on the 5th day after birth to 27,6 cm on the 10th day when the edema had just disappeared, and further to 29.7 on the 19th day after birth. It is natural to assume that this hypoproteinemia has a causal connection with the edema. The edema threshold obviously lay somewhere between 227 and 276 mm oncotic pressure.

The liver is probably the place of origin of the blood proteins. In icterus congenitus gravis there is a serious liver injury. It is not improbable that there is a similar injury of the liver also in hydrops congenitus which results in insufficient protein production. Thus these 2 etiologically closely related affections, icterus gravis and hydrops congenitus, are also brought closer together from a clinical viewpoint, and the frequently occurring transitional cases (hydrops congenitus with icterus and bile casts in the liver, icterus gravis with edema) find their explanation in the common liver injury.

### **Anemia is not an obligatory symptom of hydrops congenitus.**

The assumption originally set forth by SCHRIDDE that there is a primary hemolytic anemia in cases of fetal erythroblastosis, has since always had its adherents. More recent

investigations on the disconcordance of the blood groups between mother and child in these conditions (the Rh factor), seems to support this interpretation.

However the fact cannot be overlooked that these children are often born with a perfectly normal blood picture. Normal values for hemoglobin and red blood corpuscles have been demonstrated repeatedly in icterus gravis (4, 2, 7 et al.). The anemia does not develop until later, at the same time as the erythroblastosis disappears.

Investigations of the blood picture in hydrops congenitus are very scarce. Increased blood-pigment deposition in the reticulo-endothelial system, as an expression of increased destruction of the blood corpuscles, cannot always be demonstrated in hydrops congenitus (5). Blood examinations have been made only twice on children with hydrops congenitus born alive. These showed the following values: hmgb. 81% and 3 765 000 red blood corpuscles (5), hmgb. 120% and 3 500 000 red blood corpuscles (3). In the two cases of erythroblastosis without hydrops and icterus mentioned above (6) the values for hemoglobin and erythrocytes were normal.

In the present case of hydrops congenitus the blood picture was also normal, except for the delayed development of the cells. No anemia developed in the course of the 5 weeks the child was under observation.

It thus appears difficult to maintain the assumption that there is a primary hemolytic anemia in cases of fetal erythroblastosis. The common designation for these affections suggested by BROMAN: Morbus hemolyticus neonatorum, is therefore not a happy choice. The anemia which develops in icterus gravis and in anemia neonatorum is not a central symptom, but a subsidiary symptom to the various other symptoms of these diseases.

#### **Erythroblastosis is only temporary in hydrops congenitus.**

A peculiar and characteristic feature manifested by all children who survive fetal erythroblastosis, is the rapid disappearance of both erythroblasts and immature white blood

corpuscles in the course of the first week after birth. For some reason or other the distribution of these young cells into the blood ceases post partum and blood production is normalized in this respect, even though anemia may develop simultaneously in many cases. Erythroblastosis and anemia are clearly two completely independent results of the same noxis.

The present case illustrates that the same rapid disappearance of the erythroblasts also takes place in hydrops congenitus if the patient survives. The erythroblasts have disappeared from the peripheral blood by the 8th day and the distribution of the white blood corpuscles is normal for that age.

As a further expression that this accelerated impulse to produce blood corpuscles disappears, it is of interest to observe the simultaneous rapid decrease in the reticulocytosis which was so pronounced at birth.

### Summary.

A case is described of hydrops congenitus with erythroblastosis which resulted in cure. The edema and erythroblastosis disappeared in the course of the first week of life. A hypoproteinemia was demonstrated. The plasma proteins increased as the edema disappeared. The cause of the edema in hydrops congenitus is assumed to be a hypoproteinemia. The patient was not anemic at birth and no anemia developed post partum, which indicates that there is no primary hemolytic anemia in this condition.

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## **A Comparison of the Effects of Hospital Isolation and Home Isolation in Cases of Scarlet Fever.**

By

**AXEL STRØM.**

The question whether a scarlet fever patient, to prevent the spread of infection, ought to be isolated in hospital or whether one can be content with isolation at home, which in many cases is equivalent to no isolation at all, has long been a subject of much dispute. Whereas it was formerly usual to isolate scarlatina patients in hospital, great opposition to this procedure has been raised in recent years. The arguments advanced against it are: Firstly, that it has not been possible to establish with certainty that hospital isolation has any influence on the spread of the disease, scarlet fever being not less prevalent in places where such isolation is strictly practised than in places where it is not. Secondly, that patients with manifest scarlatina constitute only a small fraction of those infected and it therefore is unreasonable to isolate them. Thirdly, that isolation in hospital is an expensive measure which entails great outlay for the community, without yielding corresponding advantages. And fourthly, that hospital isolation in certain cases may have injurious effects, the patients being infected during their stay in the hospital by other types of streptococci than those they originally possessed and being therefore more liable to complications and recurrences.

In Oslo the great majority of the scarlet fever patients have been isolated in hospitals up to the last few years. During the great epidemics that have prevailed since 1939 it

has however been impossible to carry out this arrangement owing to want of room in the epidemic hospital. A large number of patients have had to be treated at home, and thus an opportunity has been given of comparing the effects of the two forms of isolation upon the spread of the disease.

#### **Own investigations.**

The records of the Oslo Board of Health respecting cases of scarlatina notified in the years 1939—42 have been examined. These records contain information regarding: the patient's name and address, year and date of birth, date of notification of the case, size of the dwelling, as well as number of adults and children living therein. The case records of the epidemic hospital have also been reviewed as regards the patients isolated in it.

In the period investigated 3659 cases of scarlatina were notified to the Oslo Board of Health. The notifications must be considered to have been fairly complete, so that they comprise the great majority of the manifest cases in the city. Of the notified patients 3349 lived in ordinary dwellings, 264 in various institutions (homes for children, boarding schools, reformatories, hospitals etc.), 5 were on board ships in the harbour when they got ill, and in 41 cases the residence was unknown. Only the first-mentioned group will be dealt with here.

Of the 3349 patients 2743 (81.9 per cent) were isolated in hospital, while 606 (18.1 per cent) were isolated at home (Table 1). Some few cases were first isolated at home, but were afterwards sent to hospital, either because complications arose or because other members of the family became infected. These patients are in the following reckoned among the home-isolated.

For 3104 (92.7 per cent) of the 3349 patients the size of the dwelling and the number of inmates was known. Of 2337 hospital-isolated patients 32 per cent lived in roomy or very roomy dwellings, 54.2 per cent in crowded and 13.8 per cent

Table 1.

Number of scarlatina patients isolated respectively in hospital and at home.

3349 patients notified to Oslo Board of Health in 1939-42.

Year	Number of patients		Percentage home-isolated
	Hospital-isolated	Home-isolated	
1939	905	65	6.7
1940	428	37	8.0
1941	534	347	39.4
1942	876	157	15.2
Totals	2743	606	18.1

in overcrowded dwellings. As regards the home-isolated patients the corresponding figures were: 49.7, 48.4 and 1.8 per cent. Thus in carrying out the system of isolation a certain degree of selection had been practised; it was preferably patients from »good» dwellings that had been isolated at home, while those from »unsatisfactory» and »bad» dwellings had been sent to the hospital. This circumstance must be taken into account when comparing the effects of the two forms of isolation.

Table 2.

Occurrence of single cases and multiple cases of scarlatina in the same household.

Primary case isolated	Number of patients in households with					
	1 case	2 cases	3 cases	4 cases	5 cases	Total
In hospital	2151 (78.3 %)	444 (16.2 %)	102	36	15	2748 (100 %)
At home	470 (78.2 %)	100 (16.6 %)	27	4	0	601 (100 %)
Totals	2621 (73.8 %)	544 (19.2 %)	129	40	15	3349 (100 %)

Table 2 shows the occurrence of single and multiple cases in the same household. It has been reckoned as multiple occurrence in the same household when new cases have arisen among the other members in the course of the first ten days after admission to hospital of the patient primarily attacked, or in the first three weeks after his return from the hospital. As regards the home-isolated patients, it has been reckoned as multiple occurrence when new cases have arisen in the household during isolation at home or in the first three weeks after cessation of the isolation. Cases occurring in the same household outside of these time-limits have been regarded as separate cases independent of each other. Of such cases, however, there have not been many. It appears from the table that *the frequency of multiple cases was the same in families where the primary case had been treated in hospital as where it had been isolated in the home.*

For each family there has further been reckoned the number of adults and children who have been exposed to the risk of infection and the number of secondary cases occurring among them. As »exposed to infection» have been reckoned all members of the household minus the primary case, with the exception that in case of lodgers only those who were room-mates have been regarded as »exposed».

Unfortunately the material suffers from certain defects which impair its utility for such calculations. For example, we lack particulars as to the exact age of the »exposed» persons; the only information at hand was if they were under or over 15 years old. Further, we have no knowledge as to whether any members of the household have previously had scarlet fever, and as regards the composition of the household, we only know what it was at the time of the health inspector's visit, *i. e.*, immediately after notification of the case. Finally, as regards secondary cases, we know only those notified to the public health authorities, while milder cases, where a doctor has not been consulted, have not been included in the calculations. The health authorities state that, when deciding whether a patient should be isolated at home or in



hospital, regard was paid to the question whether the other members of the family had previously had scarlatina and whether any of those most exposed to infection could move from the house during the time of isolation. Thereby the home-isolated group has undoubtedly become »better» than the group isolated in hospital, a circumstance which must be taken into consideration when judging about the figures found.

Table 3.

Frequency of secondary cases of scarlatina in households of 2573 hospital-isolated primary cases and 553 home-isolated primary cases.

	0—14 years		15 years and over	
	Hospital-isolated	Home-isolated	Hospital-isolated	Home-isolated
Number exposed to infection .	1747	264	5224	1070
Number of secondary cases . .	205	40	124	29
Number of secondary cases per 100 exposed to infection . .	$11.78 \pm 0.86$	$15.15 \pm 2.21$	$2.37 \pm 0.21$	$2.71 \pm 0.50$
Home-isolated = 100 . . . . .	77	100	87	100

Table 3 shows that, both for children and adults, the percentual frequency of secondary cases among those exposed to infection was somewhat *smaller* when the primary case was isolated in hospital than when it was isolated at home. But the difference cannot be said to be great even if due regard is paid to the dissimilarity of the two groups compared.

A closer analysis of the material showed that the comparatively small effect of hospital isolation was due to two factors: too late admission of the patients to hospital and great frequency of return cases.

Table 4 shows the day of admission for 1016 primary cases, who were admitted to the hospital in 1941 and 1942. Only about 60 per cent were admitted in the first three days of the disease and only about 90 per cent in the course of the first week. Admission took place up to the 29th day

Table 4.

Point of time in course of illness for admission to hospital.

1016 hospital-isolated primary cases of scarlatina, admitted to the hospital in 1941-42.

	Number of days that elapsed from beginning of illness till date of admission to hospital. All ages						Total
	0-1	2-3	4-5	6-7	8-14	15 and more	
Number of cases .	136	477	288	60	71	34	1016
Percentage . . . .	13.4	46.9	23.4	5.9	7.0	3.3	100.0

Table 5.

Frequency of secondary cases in households from which the primary case was sent to hospital early, medium late or late.

1016 hospital-isolated primary cases of scarlatina, admitted to the hospital in 1941 and 1942.

	Number of days elapsing from beginning of illness till date of admission to hospital. All ages		
	0-3 days	4-7	8 or more days
Number exposed to infection .	1715	774	280
Number of secondary cases <sup>1</sup> . .	53	37	24
Number of secondary cases per 100 exposed to infection . . .	3.09±0.42	4.78±0.77	8.57±1.67

after beginning of the illness. It is to be noted that here are *not* included cases which had first been isolated at home, but were afterwards sent to hospital for one or other reason. It appears from table 5 that the frequency of secondary cases among the other members of the household increases greatly according to the length of time elapsing from the outbreak of the disease until admission took place. Thus it can be no

<sup>1</sup> Return cases not included.

doubt that the belated admission has facilitated the spread of infection and reduced the effect of the hospital isolation.

As *return cases* have been reckoned cases of scarlatina occurring in a household during the first three weeks after the return from the hospital of another member of the household.

Among the 2743 patients isolated in hospital  $97 = 3.5$  per cent occasioned return cases after their discharge. The number of return cases was  $124 = 4.5$  per cent. As the total number of secondary cases occurring in the households of the patients isolated in hospital was 329 (table 3), the return cases thus constituted 37.7 per cent of the secondary cases in this group.

As to the group in which the primary case was isolated in the home, we cannot speak of return cases in the ordinary sense, but in order to get an idea of the frequency with which infection takes place after cessation of home-isolation we have calculated the number of secondary cases arising in the first three weeks after termination of the isolation. There were 10 such cases out of a total of 69 secondary cases in this group (14.5 per cent). The frequency of infection after the end of the isolation was thus considerably greater in the case of hospital-isolation than in case of isolation at home. This also appears from Table 6.

This circumstance has greatly contributed to reduce the effect of hospital isolation. This is clearly apparent from

Table 6.

Frequency of return cases in households of 2573 hospital-isolated primary cases and 553 home-isolated primary cases.

	0—14 years		15 years and more	
	Hospital-isolated	Home-isolated	Hospital-isolated	Home-isolated
Number exposed to infection . . . . .	1614	228	5152	1047
Number of return cases . . . . .	72	4	52	6
Number of return cases per 100 exposed to infection . . . . .	$4.46 \pm 0.51$	$1.75 \pm 0.87$	$1.01 \pm 0.14$	$0.57 \pm 0.23$

Table 7.

Frequency of secondary cases of scarlatina in households of 2573 hospital-isolated primary cases and 553 home-isolated primary cases.

N. B. Secondary cases occurring after termination of the isolation period are not included.

	0—14 years		15 years and more	
	Hospital-isolated	Home-isolated	Hospital-isolated	Home-isolated
Number exposed to infection .	1747	264	5224	1070
Number of secondary cases . .	133	36	72	23
Number of secondary cases per 100 exposed to infection . .	$7.61 \pm 0.63$	$13.64 \pm 2.11$	$1.38 \pm 0.16$	$2.15 \pm 0.44$
Home-isolated = 100 . . . . .	56	100	64	100

Table 7, in which is computed the risk of infection for the other members of the household *when the return cases are not taken into account*. In such case the risk of contracting the disease is considerably less in the households of hospital-isolated patients than in those of patients isolated at home. As regards children the difference is so great that it must be assumed to be real and not due to fortuities (it is 2.7 times the mean error). For adults it is only 1.67 times the mean error, but when it is taken into consideration that the home-isolated patients represent a »better» group than those isolated in hospital, it is probable that the difference is a real one also for the adults.

Owing to the important part played by the return cases in this material some further investigations of these patients have been undertaken.

In Table 8 is shown the frequency of return cases after isolation periods of varying duration. We see that both for adults and children the frequency of return cases increases with the length of the isolation time. The numbers in the separate groups are, it is true, small, but the tendency indicated by the figures is indisputable.

Table 8.

Frequency of return cases after different length of the isolation period.

1070 hospital-isolated patients, discharged from hospital in 1941 and 1942.

Length of isolation period	0—14 years			15 years and more		
	Number exposed to infection	Number of return cases	Number of return cases per 100 exposed to infection	Number exposed to infection	Number of return cases	Number of return cases per 100 exposed to infection
Up to 35 days	126	3	2.38	509	5	0.98
36 " 49 "	409	18	4.40	1331	15	1.13
50 or more "	133	7	5.26	432	7	1.62

This remarkable phenomenon finds its explanation in the fact that the patients who have been longest isolated represent complicated cases and that such patients remain longer infectious and therefore give rise to return cases much oftener than patients with non-complicated course of the disease.

Table 9.

The principal complications in 1112 cases of scarlatina, discharged from hospital in 1941 and 1942.

	Number	Per cent
Uncomplicated cases	529	47.6
Complicated cases	583	52.4
With one complication	370	33.3
With more than one complication	213	19.1
Complicated by adenitis . . . . .	292	26.8
"    "    otitis media . . . . .	162	14.6
"    "    sinusitis . . . . .	74	6.7
"    "    angina . . . . .	60	5.4
"    "    myopathy . . . . .	44	4.0
"    "    rhinitis . . . . .	35	3.1
"    "    nephritis . . . . .	29	2.6
"    "    arthritis . . . . .	19	1.7
Recurrence . . . . .	7	0.6

In Table 9 is shown the incidence of complications among 1112 cases from 1941—42, and Table 10 shows the frequency of return cases after isolation periods of varying duration in the uncomplicated and the complicated cases. Firstly, we see that, when the material is divided into cases with and without complications, the frequency of return cases does not increase with the length of the isolation period, and secondly, that the complicated cases give occasion to return cases far more often than the uncomplicated.

*Table 10.*

Frequency of return cases after different periods of isolation.  
529 uncomplicated and 583 complicated cases.

Isolation period	0—14 years			15 years and more		
	Number exposed to infection	Number of return cases	Return cases per 100 exposed to infection	Number exposed to infection	Number of return cases	Return cases per 100 exposed to infection
Uncomplicated cases						
Up to 35 days	101	3	2.97	379	2	0.58
36 » 49 »	208	2	0.96	631	4	0.63
50 or more »	14	0	0	48	0	0
Unknown	15	0	—	54	0	—
	338	5	$1.48 \pm 0.66$	1112	6	$0.54 \pm 0.22$
Complicated cases						
Up to 35 days	25	0	0	130	3	2.31
36 » 49 »	201	16	7.96	700	11	1.57
50 or more »	119	7	5.88	384	7	1.82
Unknown	12	4	—	45	3	—
	357	27	$7.56 \pm 1.40$	1259	24	$1.91 \pm 0.39$

The initial dispersion of infection was, on the other hand, the same for complicated and uncomplicated cases. The number of secondary cases among 100 persons exposed to infection was, when return cases were not included,  $3.45 \pm 0.49$  for the uncomplicated and  $3.12 \pm 0.50$  for the complicated cases.

### Discussion.

It appears from Table 7 that during the isolation period, which means as a rule the first 4 to 6 weeks after beginning of the illness, isolation in hospital is a good deal more effective in checking the spread of infection than isolation at home. The difference would probably have been found to be still greater if we had compared the effects of hospital isolation with those attained when the patients are allowed to lie at home without any form of isolation.

These results accord well with those arrived at by DOULL with respect to diphtheria. On the basis of CHAPIN's figures in the Annual Reports of the Superintendent of Health in Providence he has carried out an investigation respecting the frequency of diphtheria among family contacts of patients isolated in hospital and of those who lay at home without isolation. In the former group the frequency of secondary cases was 4.26 per cent, in the latter it was 7.42 per cent (standardized quotients).

It is also, of course, very reasonable to suppose that these diseases, which are characterized by secretion from nose and throat, involve a greater risk of infection for the other members of the household when the patient is lying at home — even though he is supposed to be »isolated» there — than when he is being treated in hospital. Therefore the frequency of secondary cases increases in proportion with the length of time that elapses from the beginning of the illness until the patient is admitted to hospital (Table 5).

But the effectivity of hospital isolation in our material has been greatly reduced on account of the return cases, although the frequency of such cases cannot be said to have been unusually great in our investigation.

It appears from Table 10 that it mainly is the complicated forms of the disease that are responsible for the return cases and the problem as to how we are to diminish the frequency of such cases, and thereby render the isolation in hospital

more effective, becomes therefore first and foremost a question of the manner of dealing with the complicated cases.

It is naturally to be expected that in an epidemic hospital comparatively many complicated cases of scarlatina will be assembled. These patients require special treatment and must therefore be sent to hospital. But in view of investigations made by GUNN and GRIFFITH, ALLISON and BROWN, ALLISON and others, we cannot disregard the possibility that the hospital isolation itself may bring about complications. The patients in the large wards may infect each other with their different types of streptococci, and such new infections or reinfections seem to have a tendency to occasion complications. LICHTENSTEIN found that of patients isolated separately, or together with brothers or sisters or playmates, 14.7 per cent got complications, 5.3 per cent had recurrences and 2.6 per cent gave occasion to return cases. The corresponding figures for those isolated in common wards were 47.1, 11.6 and 6.9 per cent. BERGMAN also arrived at the same result in an investigation of similar character.

Likewise in our material there are things which point in the same direction. If we compare the frequency of return cases after isolation at home (Table 6) and after isolation in hospital (Table 10), we see that the figures for the home-isolated patients (1.75 and 0.57 per cent) accord very well with those for uncomplicated cases isolated in hospital (1.48 and 0.54 per cent), a finding which speaks strongly for the assumption that the majority of the home-isolated cases were uncomplicated. This may be due to the cases isolated at home having been of milder character than those treated in hospital, but, as it is obviously not very easy to decide at the beginning of an illness whether the case will proceed without complications or not, we cannot disregard the possibility that some of the complications have arisen as a result of the isolation in hospital.

The logical consequence of this view is, as has been strongly maintained by BERGMAN, that hospital-isolation ought as far as possible to be arranged separately for each patient and not



in common wards. Where entirely individual isolation cannot be arranged, the patients ought to be isolated in small groups which are not allowed to come into contact with other groups while in the hospital. No new cases ought to be admitted to the room in question until the whole group has been discharged. Complicated cases ought to be as far as possible isolated separately and are always to be kept apart from the uncomplicated.

The period of isolation must be adapted to each individual case. Patients without complications may be discharged after a short isolation period (3 or 4 weeks), while in complicated cases the isolation must last longer. As the streptococci generally remain in the throat for a much longer time than that in which experience has shown it to be necessary to isolate the patients, we have only the clinical symptoms to guide us when deciding whether a patient can be discharged or not. As a general principle, it must be demanded that all clinical symptoms shall have disappeared, especially that the mucous membranes are normal, before the patient is discharged. This accords with the mode of procedure in cases of diphtheria, where it is now usual to lay more weight on the demand that the patient shall be clinically cured than that the nose- and throat cultures shall be negative, at all events when dealing with adults. As it occasionally happens that complications do not arise until after the patient has been discharged, it is advisable for patients to avoid contact with children as far as possible during the first time after return from hospital and to consult a doctor if they should get ill again.

The dispute as to whether or not we should adopt isolation in hospital in cases of scarlatina is to a large extent due to uncertainty as to what can be attained by such isolation. Owing to the numerous abortive cases and the many healthy carriers it is impossible to eradicate scarlatina by isolation of those suffering from the disease. The most one can attain is to diminish the risk of infection and the frequency of illness among those most exposed to danger, *i. e.*, the

members of the patient's household. The reason why these latter are more exposed than people in general is that the patients undoubtedly offer more danger of infection than healthy carriers. The situation must be assumed to be similar to that found by DOULL and collaborators as regards diphtheria. According to the results of their investigations the frequency of secondary cases among family contacts of a patient was ten times greater than among the contacts of a carrier.

So long as we have no other and more effective method of protecting the patient's associates it can hardly be deemed justifiable to reject the protection which isolation in hospital represents. But the necessary presumption must be that we are in a position to arrange the isolation in accordance with the principles stated above. If this cannot be done, the total effect of hospital-isolation will be so slight that it cannot be deemed economically defensible to maintain the system. Moreover we also run the risk of exposing the patients to new infections or reinfections during their stay in the hospital.

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## Non-traumatic subarachnoid Hemorrhages in Children beyond the Neo-Natal Age.

By

SVEN BRANDT.

Non-traumatic (»spontaneous») subarachnoid hemorrhages are acute hemorrhages in the subarachnoid space resulting in bloody spinal fluid and due to abnormalities of the vessels between the pia mater and the arachnoidea, what with known, what with unknown origin. Medical science has been acquainted with them since the middle of the last century, but it is only in the last few decades that the disease has been recognised as a *clinically* well defined, acute affection, often in apparently sound individuals. Its cause, though, is only partly known and probably multifarious; but that it to some extent is a question of pathologic conditions in the brain different from those that cause the ordinary apoplexy in older subjects is indubitable, as proved also by the fact, among others, that a very large proportion of the patients are young people.

It is claimed the disease is rare in children (ROEMCKE), especially in children under 3 years of age (CATEL, HESS, SECKEL); but it is my experience that it *may* occur, even in infants. In the following I shall describe such a case and, on the background of a number of previously reported cases, discuss the question of non-traumatic subarachnoid hemorrhages in children and their cause.

### Case History.

The patient, a girl a little under 7 months old, was admitted with signs of acute meningeal hemorrhage. She was the youngest child of two. She had been born at term, easily and *per naturam*.

Her weight at birth was 3200 grams. Since she was 3 months old she had been fed artificially and was now getting five meals a day, of ordinary, by no means uniform spoon-fed children's food, besides codliver oil every day. She thrived well, and had hitherto been quite healthy. On the day of admission she had been a little languid, had no appetite and once vomited a little mucus, but when the mother left her she had nevertheless been smiling, lively and not at all in bad condition. The mother was absent for ten or fifteen minutes, but was then fetched by the maid, who said the child had suddenly become sick. When the physician arrived she was unconscious, an adrenalin injection was given, and she was immediately brought to the hospital.

On arrival there she was almost moribund; the extremities were rather cold, the pulse could not be felt, the temperature was 35.9 C. After stimulation with sympatol and nicetamid she picked up a little, but she was soporose, whined, slabbered and sighed. The eyes moved slowly from side to side, the neck was stiff and the fontanel tense. Now and then there were tonic spasms, the fingers were spread and the hands pronated; but between the spasms the extremities were moved freely, and there were no signs of paralysis. The patellar reflexes were lively. The rest of the objective examination showed nothing abnormal, except that the heart action was 200. Especially, there were no signs of outward violence, and no bleeding from ears or nose.

Lumbar puncture produced under strong pressure spinal fluid of a color like highly diluted raspberry juice. It was of that tinge during the whole of the evacuation, only at the very last it became a little more bloody. Microscopy showed many erythrocytes and only a few leukocytes. There was no xanthochromia and no clotting. — *Blood sugar* immediately after admission: 0.310 per cent. — *Urine*: + sugar, ÷ albumen, ÷ erythrocytes, ÷ diacetic acid, + acetone.

After the lumbar puncture, the child revived just a little, but 5 hours after admission the condition was nevertheless more or less the same; the pulse was very rapid, she regurgitated blood and was pale and whining. *Suboccipital puncture* now produced very bloody spinal fluid during the entire evacuation. In spite of further treatment with sympatol, nicetamid and saline solution she declined, and towards morning, 11 hours after admission, she died. Permission to necropsy was refused.

*Epicrisis.* — A hitherto healthy child, 7 months old, suddenly becomes sick, with unconsciousness, symptoms referable to the meninges, bloody spinal fluid and later bloody vomit-

Table 1.

Year	Author	Age	Sex	Preceding Symptoms	Clinical Manifestations	Death (†) or Recovery
1 1869	GINTRAC/VIDAL	2			Convulsions, vomiting, strabismus	†
2 »	» /BARTHEZ and RILLIET	12	♀	Uncharact. symptoms through one year	Sudden unconsciousness and hemiplegia. Improvement. Later relapse with hemichorea.	†
3 »	» /MORGAGNI	14	♂		Sudden vomiting, headache, loss of speech and motions.	†
4 »	» /LOMBARD and al.	13	♀		Sudden universal convulsions.	†
5 »	» /HERVIEUX	5	♀		Hemiplegia → Tetraplegia.	†
6 »	»	3	♂		Sudden screaming, convulsions and vomiting.	†
7 »	»	14	♂		Sudden meningeal signs → coma, clonic spasms of left hand.	†
8 »	»	8	♀		Shivering fever, headache, dimness, vomiting, convulsions.	†
9 1871	HAUSER	4	♂		Death in attack of pertussis.	†
10 1900	MOIZARD and BACALOGU (cit. EHRENBURG)	7	♂		Meningeal signs, anisocoria, pupils fixed to light. Later convulsions and exitus.	†
11 1904	FROIN	14				†
12 1908	BOUQUET	14	♂		Meningeal signs.	r
13 »	NETTER and CLERC (cit. of EHRENBURG)	10	♂		Sudden unconsciousness following climbing.	†
14 1912	GRIOLET (cit. EHRENBURG)	12	♂	Headache, vomiting	Sudden unconsciousness with meningeal signs, contractures and transitory palsies.	r
15 1921	BASS	7/12			Meningeal signs.	†
16 »	»	?			Convulsions, delirium, coma.	†
17 »	»	?			» » »	†

I.

Death (†) or Recovery (r)	Duration	Relapse	Pathologic Findings (Necropsy or Spinal Fluid)	Facts of sure or possible etiologic Importance
†			Large clot in the subarachnoid space	
†	3 1/2 m.		Clot covering the left hemisphere	
†	12 hs.		Blood on the cerebellar surface	Already addict to ardent spirits. — Epistaxis
†	19 hs.		Hemorrhages in the brain and on the cerebral surface	Pneumonia. — Preceding enteritis
†	7 ds.		Hemorrhages on both hemispheres. Small hemorrhages in the cerebrum	Jaundice, sclerema. (Hemorrhagic diathesis?)
†	0 ds.		Subpial- and arachnoid hemorrhages	
†	12 hs.		Clot on the cerebral base between the optic tract and the cortex	Previously often suffered from headache
†	3 ds.		Subpial and subarachnoid hemorrhage on the frontal lobe. Venous congestion	Infectious disease? Poisoning?
†			Subarachnoid hemorrhage from a large ruptured vessel	Valvular heart disease. Embolic aneurysm? Pertussis?
†	1 d.		The brain covered by blood	Hemophilia
†			Hemorrhages in the mid-brain and in the subarachnoid space	Meningitis?
r			Bloody spinal fluid	Insolation
†	0 ds.		Subarachnoid hemorrhage on the base around the brain stem	
r			Bloody spinal fluid	
†			Large hemorrhage on the brain surface	Acute leukemia
†			Bloody spinal fluid	" "
†			" " "	" "

	Year	Author	Age	Sex	Preceding Symptoms	Clinical Manifestations
18	1923	GOLDFLAM	10	♀		Headache, unconsciousness, pyramidal signs.
19	"	"	8	♀		
20	"	"	10	♂		Sudden headache and unconsciousness.
21	1924	ZYLBERLAST-ZAND (cit. SECKEL)	2			
22	1926	HERMAN	11	♂		Sudden unconsciousness following terror.
23	"	"	14	♀	Paleness, headache for one day	1) Aggravation of headache--coma, constant for 6 hours. 2) Relapse with hemiparesis.
24	"	MUNCH	14	♂		Immediate death, following insignificant trauma.
25	1928	BARBER and TAYLOR	13			
26	"	MARTINEZ	12	♂		Unconsciousness, meningeal signs Positive Babinski's sign.
27	1929	BENHOLDT-TOMSEN	8/12			(Pertussis)
28	"	"	6			(Pneumonia)
29	"	"	1			No clinic informations.
30	"	"	2			
31	"	RÖMCKE and USTVEDT	12	♂		
32	1931	SECKEL	12	♀	+	Sudden headache, vomiting, dimness, meningeal signs, diplopia, temporary polyuria.
33	"	"	10	♀		Meningeal signs with sudden aggravation. Later: fever, bradycardia, paresthesias, radicular pains.
34	1933	INGEBREGTSEN/RÖMCKE	11			Sudden meningeal signs, loss of consciousness.
						While playing became suddenly restless, vomiting turbid.

Death (†) or Recovery

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(Tab. 1. Cont.)

Death (+) or Recovery (-)	Duration	Relapse	Pathologic Findings (Necropsy or Spinal Fluid)	Facts of sure or possible etiologic Importance
r	short		Bloody spinal fluid	Later attacks of migraine and fainting spells.
r			" " "	
r	short		" " "	
r			" " "	
r	short		" " "	
r		+	" " "	Epistaxis.
†			Subarachnoid hemorrhage on the base of the brain	
	some weeks		Bloody spinal fluid	
r			" " "	Syphilis.
†			Hemorrhage on the l. hemisphere	Pertussis.
†			Subarachnoid hemorrhage, venous thrombosis, vascular congestion	Infectious disease.
†			Meningeal hemorrhage, venous throm- bosis	Infectious disease?
†			Hemorrhagic leptomeningitis, venous congestion and thrombosis	Infectious disease?
r			Bloody spinal fluid	So-called »encephalitis» 4 years before.
r	10 ds.		Bloody and yellow spinal fluid	Asthenic circulatory con- stitution.
r	2 1/3 ms.	+	" " " " "	Asthenic, some infantile con- stitution. Often headache.
r	short		Hemorrhage around the pons and in the fourth ventricle	



	Year	Author	Age	Sex	Preceding Symptoms	Clinical Manifestations
35	1938	LYNGAR	3	♀		1) Sudden tumbling, headache, meningeal signs. Hemiplegia, 2) Sudden meningeal symptoms → coma, pyramidal signs, pupils fixed to light.
36	"	"	9/12	♂		Crying, asomnia. Retinal hemorrhages (No meningeal signs).
37	1939	CASANBON and CUCULLO	12			
38	"	CATEL	12	♀		While playing became suddenly pale, with headache, meningeal signs, retinal hemorrhages. The following day: hemiplegia.
39	"	"	3	♂		(Hemangioma nuchae) Convulsions, meningeal signs.
40	"	IRISH	7	♂		
41	"	"	2/12	♂		(Pertussis).
42	"	COCKAGNE	11/12	♂	Vomiting, pallor, limpness during one week.	At arrival comatous with bulging fontanel.
43	"	ENGELHARDT	11	♂		While playing suddenly ill with meningeal signs and convulsions.
44	"	JELKE	8/12	♀		Meningeal signs, convulsions, spastic hemiplegia.
45	"	HALLEZ	7	♂		Sudden meningeal signs. Albuminuria.
46	"	SACCA	10	♀		Sudden meningeal signs.

(Tab. 1. Cont.)

Death (†) or Recovery (r)	Duration	Relapse	Pathologic Findings (Necropsy or Spinal Fluid)	Facts of sure or possible etiologic Importance
r	22 ds.	+	Bloody and yellow spinal fluid	
r	short		" " " " "	
r		+	Relapsing meningeal hemorrhages	Later hemoptysis, positive tub. test. (No radiol. changes). The mother had died of tuberculosis.
r	short		Bloody spinal fluid. Arteriographic signs on aneurysm	Aneurysm?
r			Bloody and yellow spinal fluid	Fits of convulsions for years. Sturge-Webers disease?
†			Tuberculous meningitis with pial and arachnoid hemorrhages	Tuberculous meningitis.
†			Subarachnoid hemorrhage	Pertussis.
r			Bloody spinal fluid. Retinal hemorrhages	(Bleeding and clotting times normal).
r	6 ws.		Bloody spinal fluid	Scurvy??
†			Subarachnoid hemorrh. on the r. hemisphere	Acute leukemia.
r	18 ds.	+++ (6)	Bloody spinal fluid. Operation after the 4th attack showed a cyst in the arachnoida, with spinal blockade.	
r	10 ds.		Bloody spinal fluid with rather plenty of white cells	

	Year	Author	Age	Sex	Preceding Symptoms	Clinical Manifestations
47	1939	SEGERS	11	♂		Clinical information not available.
48	1940	PLUM	3/12	♂		Suddenly ill with convulsions, vomiting, loss of consciousness. Hypoprotebinemia.
49	1941	FANCONI	4/12	♂		Sudden shriek, convulsions, apathy, unconsciousness, albuminuria, glucosuria, acetoneuria. Hypoprotebinemia.
50	"	STEFFENONI	13	♂		Epistaxis, giddiness, meningeal signs, papilledema, facial paralysis.
51	"	WATANABE	5	♂		
52	1942	HESS/TAU CHIUN WU	10	♀		Sudden vomiting, convulsions, retinal hemorrhage. Unconsciousness for 8 days.
53	"	HESS	12	♂	Headache, vomiting, following fall without cranial trauma.	After some improvement, on the third day sudden meningeal signs and pyramidal signs.
54	"	HESS/TAU CHIUN WU	12	♂		Meningeal signs, unconsciousness for 5 days. (Acute rhinitis, fever).
55	"	"	12	♀		Sudden meningeal signs. Albuminuria.
56	"	"	1 1/2			Beyond retinal hemorrhages no clinical information.
57	"	"	9	♀		Meningeal signs, unconsciousness, delirium.
58	1945	BRANDT	4	♂		Coma, spastic tetraplegia, convulsions, retinal hemorrhages.
59	1944	Author's Case	7/12	♀	Loss of appetite, languor, vomiting	Meningeal signs, convulsions, unconsciousness, glucosuria, acetoneuria.

Death (†) or

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(Tab. 1. Cont.)

Death (+) or Recovery (-)	Duration	Relapse	Pathologic Findings (Necropsy or Spinal Fluid)	Facts of sure or possible etiologic Importance
r	few ws.		Bloody spinal fluid	Vitamin K deficiency.
r			" " "	Vitamin K deficiency.
†			Sarcomatous tumours in the meninges	Diffuse sarcomatosis.
†		+	Meningeal hemorrhage	Idiopathic thrombopenic purpura.
r	1 1/2 ms.		Bloody spinal fluid	
r		+	Bloody and yellow spinal fluid	
†			Bloody spinal fluid	Infection?
r	24 ds.	+	" " "	
r	46 ds.			
r	26 ds.		" " "	
†			Bloody spinal fluid. Leukemic infiltration in pons with cerebrospinal hemorrhage	Acute leukemia.
†			Bloody spinal fluid	Hemorrhagic diathesis?

ing; there is hyperglycemia, glycosuria, acetonuria and tachycardia, and death survenes 11 hours after admission.

About the cause of the subarachnoid hemorrhage it is hardly possible to conclude anything with certainty on the basis of the given data. The early symptoms in the form of languor and lack of appetite a few hours before do not exclude, but make it less likely, that it has been a case of arterial rupture (aneurysm or vascular tumor). The bloody vomiting observed later might perhaps point to a hemorrhagic diathesis, but about the exact nature of this (? hypoprothrombinemia, blood disease) the time was too short to find out anything.

### Discussion.

As already said, the disease is much rarer in children than in adults. Thus, FROIN found only 1 case in a child (14 years old) among a material of 27 cases. STRAUSS and co-workers have, among 34 cases, no children, ROEMCKE & USTVEDT among 27 cases 1 child, LASSEN & VANGGAARD among 43 cases 6 in ages between 10 and 20 years, BRUSTAD & VOGT among 55 cases 4 in ages between 11 and 20, LETH-PETERSEN no children among a material of 27 cases. (It is possible, though, that in some cases special distribution-conditions may have been determining for whether the materials included any children or not). The first cases from a pediatric service were communicated by SECKEL, in 1931, and later a number of cases have been collected and communicated by CATEL (1939) and URSULA HESS (1942).

In Table 1 is given a list of 59 cases in children up to the age of 14 years, most of them compiled from the literature covering subarachnoid hemorrhages. Cases of verified aneurysm are not included. A number of children could not be included, because their cases formed part of larger materials, in which the individual case histories were not given in any detail. The diagnosis was in all cases established either by examination of the spinal fluid or at necropsy. All the oldest cases figuring in the table are from the time before

the introduction of spinal puncture, and thus include only cases with lethal issue, because in those days it has hardly been possible to diagnose those which eventually were cured. I have preferred the designation »non-traumatic» to »spontaneous», because the latter term is used so differently: now as identical with »non-traumatic», now again as expression only for those subarachnoid hemorrhages for which no plausible explanation can be found (rather covering GOLDFLAM's term »angioneurotic» subarachnoid hemorrhages).

Clinically, it is hardly possible to distinguish a primary subarachnoid hemorrhage from a hemorrhage in the brain itself with complicating subarachnoid bleeding (ANTONI); though in some cases it has been done (EHRENBERG). Subdural hemorrhages, (in german literature known as *Pachymeningosis hæmorrhagica interna*) on the other hand, very seldom break through to the subarachnoid space. ROSENBERG (quoted by EHRENBERG) found normal liquor in 32 children with pachymeningosis, and only in 2 cases later irruption into the subarachnoid space.

#### Age and Sex.

Table 2 shows the distribution of the cases on boys and girls in the different age groups. It may seem as if the disease in children were most frequent in the first years of life and towards the age of puberty. From the respective incidence in boys and girls it is hardly possible to draw any sure conclusions, since in so many of the cases there is no information about the sex of the child.

Table 2.

Age	0—4	5—9	10—14	?	Total
♂	9	4	15	—	28
♀	3	4	10	—	17
Sex?	7	1	4	2	14
Total	19	9	29	2	59

### Clinical Features.

The clinical picture of the disease in children is in its main features the same as seen in adults. Among the many excellent descriptions of this very alarming syndrome there is reason especially to mention EHRENBURG's (1924 and 1936). Outstanding features are symptoms of sudden veiling of the consciousness and signs of meningeal irritation. In most cases, but not always, both these symptoms are present. Not infrequently, the patient is in coma from the beginning, and the meningeal symptoms do not become marked until after consciousness returns. In one respect the picture in children seems to differ from the one seen in adults: *convulsions* and *spasms* are more frequent. Such were observed in 17 of 47 children about whose symptoms it has been possible to get information (cf. LASSEN & VANGGAARD, 5 of 43 patients; BRUSTAD & VOGT, 5 of 55). This seems to accord well with the old experience that irritation of the central nervous system much oftener gives rise to cramps in children than in adults.

*Paralysis* and *pyramidal signs* may be present, especially if the hemorrhage extends to the hemispheres (2, 5, 14, 18, 23, 26, 35, 38, 44, 53)<sup>1</sup>. It is characteristic that they are slight and passing. If the paralysis is more massive, the subarachnoid hemorrhage is probably secondary to cerebral. The course of the disease may thus be determining for the diagnosis between primary and secondary subarachnoid hemorrhage.

*Visual disturbances* may occur in the form of blindness, hemianopsia and paralysis of the eye muscles. They, too, are light and passing. Ophthalmoscopy may disclose signs of papilledema and especially of retinal hemorrhages, which often are present without the patient having had any subjective feeling of disturbed vision (LYNGAR) (36, 38, 50, 52, 56, 58).

*Hypoglycemia*, with glycosuria, occurs, as sign of irritation of the vegetative center. It is important to bear this in mind

<sup>1</sup> The number refers to the correspondant case no. in Table 1.

in case of comatose patients, where the possibility of diabetes must be considered (49, 59) (EHRENBERG, ROEMCKE & USTVEDT, HANSEN & VAN STAA, BRUSTAD & VOGT, and others). Something similar is the case as regards albuminuria, the presence of which may make one believe that the coma is uremic (45, 49, 55). A curious *increase of the diuresis* in ROEMCKE & USTVEDT's patient must no doubt be ascribed to irritation of the hypophysis and hypothalamus (31). It began on the third day and lasted 12 days. The maximum excretion was 3550 cc. in 24 hours. A similar observation was made by BRUSTAD & VOGT in an adult. *Acetonuria* was found in 2 children (49, 59).

Fever is seldom present from the beginning unless it is expression for a concomitant infection; but in the following days there is often a rise in temperature. This is probably a blood-resorption phenomenon, but may perhaps in some cases be an expression for irritation of the vegetative center.

The symptoms usually set in quite suddenly, in individuals who up to then had been perfectly well. It seems, however, — as pointed out especially by HANSEN & VAN STAA, — that in a number of cases prodromal symptoms could be demonstrated in the form of headaches, vomitings, lack of appetite and languor (see 14, 23, 32, 44, 53, 59).

#### Prognosis.

Since QUINCK's introduction of spinal puncture, in 1891, it has been possibly to establish the diagnosis during life, and has thus also become possible to form an estimate of the prognosis. Of the 50 cases in Table 1 from the period after 1900, 20 (= 40 per cent) had a lethal issue. The prognosis in the individual case cannot readily be given in the first days. Long lasting unconsciousness and massive focal symptoms are, as a rule, bad prognostic signs, but not necessarily so (see 52). Otherwise, the forecast depends, of course, on the cause of the subarachnoid hemorrhage; — it must be remembered that the pathologic picture is only a syndrome, not an etiologic entity.

*Relapses* were seen in 8 of the 29 children who did not



die. They occurred from 8 days to several years after the first attack. HALLEZ's patient had 6 relapses in the course of five and a half years, and every time recovered.

Lasting *after-effects* have seldom been observed, because most of the cases were not followed. In PLUM's patient, incipient hydrocephalus could be demonstrated already before the child left the hospital. In one of HERMAN's patients, a 14-year old girl (23), the condition was for a long time marked by stereotypies, dysphasia, childish speech, apathy and lack of concentration. A follow-up, by BRUSTAD & VOGT, of 41 surviving patients, most of them adult, showed that in 8 the capacity for work was much reduced, in 14 it was somewhat reduced, with marked complaints (of headaches, vertigo, loss of memory, listlessness, fatigue, paresthesias); while 19 were capable of work and apparently free from symptoms.

#### Diagnosis.

If the child shows symptoms of meningeal irritation, the diagnosis is easy; but in the absence of such symptoms, and if the patient is unconscious, it does not immediately occur to one to examine the spinal fluid. If there, moreover, is glycosuria or albuminuria, one is easily led on a wrong track, unless one makes it a rule *always* to make that examination if a child is unconscious or comatose and the anamnesis does not give grounds for supposing some other disease. *The examination of the spinal fluid is thus the key to the diagnosis.* The typical finding is a more or less blood-tinged fluid, which is evacuated under increased pressure. The immixture of blood will in case of subarachnoid hemorrhage, — in contrast to what is the case in artificial bleeding, where it is strongest in the beginning, — be the same during the whole evacuation; or rather, — if lumbar puncture is used, — stronger in the last glass, because the hemorrhage comes from the higher part of the subarachnoid space. In small infants, suboccipital puncture will often be preferable, because artificial hemorrhage is easier avoided.

If the hemorrhage is old, the spinal fluid will after centrifuging be more or less yellow. The erythrocytes may have become dissolved or may partly still be present. As a rule, there is during the following days a reactive increase in the number of white cells in the spinal fluid, the patient getting aseptic meningitis with increase of the fluid. If the diagnosis of non-traumatic hemorrhage has been established, one must not, however, rest content with this, but must try to establish also the etiologic diagnosis, because the latter may have an influence on the question of what therapy should be employed.

### **Etiology.**

The causes of this clinical picture are of many kinds, and the different etiologic factors are probably not in children equally frequent in all age classes. The causes of non-traumatic subarachnoid hemorrhage can only be demonstrated in some of the cases. In 11 of the 59 children in Table 1, the condition could be explained as the result of an existing hemorrhagic diathesis, thus by acute leukosis (15, 16, 17, 44, 58), idiopathic thrombopenic purpura (51), hemophilia (10), vitamin K deficiency (48, 49, and perhaps 5 and 59). ENGELHARDT believes that his patient (43) suffered from Vitamin C deficiency but the reader does not feel quite sure that this was the cause of the subarachnoid hemorrhage. One child (26) had congenital lues (? luetic aneurysm), and 1 (40) tuberculous meningitis. In the last case, the subarachnoid hemorrhage has probably been the result of a toxic lesion of the walls of the vessels. Something similar may have been the cause in 7 other cases, in which there were signs of infection either generalised or local in the central nervous system or its sheaths (4, 8, 11, 28, 30, 54). In 1 (50) there was diffuse sarcomatosis of the meninges, and 1 (34) probably had Sturge-Weber's disease, so that the subarachnoid hemorrhage probably was due to rupture of an intracranial hemangioma. In 1 case (12) insolation is given as the causative factor; if that is correct one must think that there has been a thermic

lesion of a vessel wall, with diapedesis. In 3 cases (9, 27, 41), whooping-cough is stated as the cause. I shall not discuss here whether it also in these cases, as supposed by some, has been a question of toxic-infectious lesion of vessel walls, or of rupture of aneurysms caused by the violent attacks of coughing. Of these HAUNER's patient (9) suffered from cardiac hypertrophy and valvular disorder, and may very likely have had an embolic aneurysm.

The rest of the cases come under the group of what by many have been termed »idiopathic» subarachnoid hemorrhages, about the cause of which there has been no end of discussion. GOLDFLAM, RICHTER, EHRENBURG and others have believed that not a few subarachnoid hemorrhages are due to diapedesis in specially disposed individuals. They suppose that the permeability of the vessels for formed elements of the blood is subject to nervous regulation, and that in some individuals this regulation may sometimes fail, with the result that the permeability becomes enormously increased (GOLDFLAM's »angioneurotic» subarachnoid hemorrhage). The subarachnoid hemorrhages are compared to the often just as inexplicable nasal and conjunctival hemorrhages in such individuals. These patients should show such symptoms as migraine, epilepsy, recurrent headaches, tendency to epistaxis and asthenic habitus. To this it must, however, be said that several of those symptoms have been present also in patients whose subarachnoid hemorrhage later, at necropsy, was found to be due to a ruptured aneurysm. Such symptoms are mentioned in the case histories of 6 of the children in Table 1 (3, 7, 18, 23, 32, 33).

Though diapedetic hemorrhages may develop very rapidly (cf. MUNCH-PETERSEN, among others), one cannot help thinking that the violent, suddenly oncoming symptoms in children who to all appearances are perfectly healthy must be due to some »vascular catastrophe», it is: rupture of a vessel that owing to some cause or other has not been able to withstand normal physiologic increases of pressure. Such a rupture can only occur if the vessel has already undergone a pathologic change. In perfectly sound arteries, an increase of the intra-

arterial pressure will not cause rupture, even if it occurs rather suddenly as the result of muscular strain; but if the vessel is pathologically altered, the increased pressure may, of course, be the performing cause of a rupture. In children, *congenital arterial aneurysm* is probably the pathologic vascular change of which there oftenest will be question; whereas acquired aneurysms (due to lues, juvenile atheromatosis, emboli from endocardiac foci or after a septic arteritis) are probably rarer, perhaps with exception of embolic, or, as many term them: mycotic, aneurysms.

It is probably now agreed by most that subarachnoid hemorrhages, at least when the question is chiefly of adults, are oftenest due to rupture of a basilar intracranial aneurysm (ANTONI, ENGELHARDT, STRAUSS, BIEMOND & TER BRAAK). HANSEN & VAN STAA found ruptured aneurysms in 19 of 22 (= 90 per cent) cases that came to necropsy; from which it would hardly be warranted, though, to conclude that about 90 per cent of all cases of subarachnoid hemorrhage, lethal and cured, are due to that cause. Their finding may also signify that the mortality is greater when ruptured aneurysm is the cause than when the condition is due to one of the different other non-traumatic causes that may produce subarachnoid hemorrhage.

Verified cases of rupture aneurysm in children are very rare. As said, they have not been included in Table 1. DONALD & KORB have in 1939 compiled from the literature 1125 verified cases of intracranial aneurysms. Among these there are 33 in children 14 years old or less (3 of them reported by Danish authors: M. SCHMIDT, 1930, PEDERSEN, 1931, ORTMANN, 1932). In 30 of the 33, the aneurysm had ruptured. To these must now be added two other cases: BJØRN HANSEN's (1933) and Mc GREGOR's (1940)<sup>1</sup>.

<sup>1</sup> Quite recently, ÅKERÉN has reported (Acta Paediatrica 1943, p. 124) a case of severe subarachnoid hemorrhage in a 6-year old boy, who ten years later got epileptic seizures. On operation, the cause of these was found to be an arteriovenous aneurysm of the right frontal lobe. The diagnosis had been established by encephalography and arteriography.

Table 3.

Age	0—4	5—9	10—14	?	Total
Children with verified ruptured aneurysms (Mc. Donald and Korb and others) . . . . .	2	10	17	1	30
Children with non-traumatic subarachnoid hemorrhages of unknown origin (= "idiopathic s. h.") . . . . .	7	3	22	—	32

Table 3 shows that the age distribution is in the main the same for children with verified rupture of aneurysms and for children with subarachnoid hemorrhages of unknown etiology («idiopathic» cases). Of course, no sure conclusions can be drawn from so small figures; still, it is noticeable that in both groups most of the cases are in children approaching the age of puberty. Of the 32 children in whom the etiology of the disease was unknown, 8 died, and in none of the cases did the necropsy show any aneurysm. In 2 cases (1, 6) the exact location of the hemorrhage was not stated, in one (2) it was over the left hemisphere, in one (3) over the cerebellum. In 4 cases (7, 13, 24, 34) the hemorrhage was at the base of the brain, around Willis's circle, just where the largest number of aneurysms, by far, occur; and though in these cases the place where the hemorrhage started was not found, it may very well have been a small aneurysm; since such, as pointed out by HARBITZ, MUNCH, and others, can often only be demonstrated by the use of an exceedingly careful technic of examination.

Interesting observations respecting the pathogenesis of congenital aneurysms and other malformations of the vessels at the base of the brain have been made by BUSSE, ASK-UPMARK, and FORBUS. BUSSE, for instance, has shown that the structure of Willis's circle differs enormously from one individual to another; anastomoses, asymmetric caliber and aneurysms are found in numerous cases. ASK-UPMARK has called attention to the special ontogenetic evolution of the basilar arteries,

according to which aneurysms may be conceived as »intended, but not completed bud-formations and branches of the vessels in question». FORBUS has been able to demonstrate, anatomically, even in fetuses, weak points in the arteries, at the points of their bifurcation, owing to defective fusion of the primitive muscularis of the artery and of its branches (»media-defects»); and he has been able to demonstrate at these points incipient aneurysms, which occur when the insufficiently supported internal elastic membrane yields to the hydrostatic pressure, which, as he also shows, is greatest at the points of bifurcation.

Will it be possible, then, to determine if a non-lethal subarachnoid hemorrhage in an individual who has not hitherto presented any symptoms, is the result of bursting of an aneurysm?

In a few such cases, arteriography may perhaps help to answer the question. Thus, in the patient case 40 (in Table 1) it was believed that an aneurysm could be demonstrated arteriographically. How much will be gained diagnostically, and perhaps also for the therapy, by that procedure, it will be for the future to find out.

To sum up, it may be said that in about fifty per cent of cases the cause of subarachnoid hemorrhage in a child is demonstrable or likely (hemorrhagic diathesis, infection, hemangioma, lues and meningitis. ? toxic-infectious lesion of vessel wall). Hematologic examination (with determination of bleeding-, clotting- and prothrombin times, thrombocyte count and Wassermann reaction), together with an evaluation of the whole clinical picture (signs of infectious disease or Sturge-Weber's disease, cultivation from the spinal fluid, and the number of white cells in the latter) will be determining for the etiologic diagnosis in the individual case.

In the other half of cases, no etiologic factors can be demonstrated. In a great many of these the subarachnoid hemorrhage will probably be due to rupture of an aneurysm of the basilar arteries; perhaps arteriography may confirm such a diagnosis.

The possibility that in specially disposed individuals the cause may be a diapedesic hemorrhage due to vasomotoric disturbances can not be denied. A review of the cases of subarachnoid hemorrhages in children do not lend much support to the supposition; the theory is interesting, but difficult to prove.

### Therapy.

The treatment of subarachnoid hemorrhages consists in confinement to bed and lumbar punctures. These may counteract the cerebral stasis and anoxemia; but there is no doubt some risk that the hemorrhage may recur. It will therefore be best that the lumbar punctures are done under control of the pressure of the spinal fluid. If lumbar puncture for technical reasons cannot be done, — in the case of infants, for instance, — suboccipital puncture should be attempted. It is in many cases much easier to perform. The object with the repeated spinal punctures is not so much to evacuate a quantity of fluid corresponding to the magnitude of the hemorrhage, as to counteract the increased secretion of spinal fluid, — the aseptic meningitis, — which always follows a subarachnoid hemorrhage.

Sometimes, though not often, there may be question of surgical intervention, if diverse after-effects indicate that the coagulated blood has not become resorbed but presses on the base of the brain or cerebral nerves. Otherwise, the therapy in the individual case will be causal, depending on the etiology (K-vitamin preparations, blood transfusion, antiluetic treatment, ascorbic acid, chemotherapeutics).

Finally there may perhaps be particular reason to call attention to the fact that hypoprothrombinemia even in older infants is an etiologic factor which must be borne in mind, especially because there is possibility for instituting a rational therapy, if the subarachnoid hemorrhage has been due to K-avitaminosis.

### Summary.

The author points out that subarachnoid hemorrhages are considerably rarer in children than in adults. He has collected 58 cases from the literature, and adds to these a case observed by himself. Besides, there are in the literature reported a little over 30 cases of subarachnoid hemorrhage due to rupture of an intracranial aneurysm. The disease is seen in children of all ages, oftenest towards the age of puberty, though in about one-third of cases in children under 4 years old. He describes the symptoms and emphasises that in the case of children who suddenly become unconscious examination of the spinal fluid should always be done. The prognosis cannot be given until the disease has lasted some days. About 60 per cent recover. Not a few of these (in his material 8 of 29) get recurrences; follow-up examinations in adult cases but not made among children seem to show that also the possibility of more or less lasting after-effects must be counted with in some cases.

The cause of the hemorrhage can be demonstrated with more or less certainty in about 50 per cent of the cases. The author calls particular attention to the fact that K-avitaminosis was the indubitable cause in 2 cases of infants, 3—4 months old. In the remaining 50 per cent, the cause was probably rupture of an aneurysm; whereas diapedesic hemorrhage on angioneurotic basis can hardly, — except perhaps in a couple of cases, — be thought in children to be as important an etiologic factor as several authors believe it to be in adults.

The treatment consists in regulation of the pressure in the subarachnoid space by means of repeated evacuations of spinal fluid. In special cases blood transfusion, vitamin-K, antiluetic treatment and chemotherapeutic remedies will be the causal treatment. So far as possible, the etiologic diagnosis should therefore always be established.

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## **«Pre-excitation» of the ventricular part of the heart and its occurrence in children.**

By

**JOHN LIND.**

In 1930, WOLFF, PARKINSON and WHITE published a report on 11, now classical, cases of »bundle branch block» which were entirely different from those previously described. These patients were in the main young »healthy» persons yielding normal radiograms of the heart and without any earlier symptoms from the heart except in one important respect, viz. a tendency to attacks of heart palpitation of the type known as paroxysmal tachycardia. The electrocardiograms showed a characteristic combination of a shortened conduction time — as it was then interpreted — and bundle branch block. The P-waves were positive in all leads. The abnormal complexes sometimes alternated with normal, or nearly normal, complexes, and during the attacks of tachycardia the QRS complex was either of the normal or the bundle branch block type. The prognosis seemed to be good, and the pathogenesis was thought to be an intraventricular blockage resulting from vagal preponderance, because in several cases it had been possible to produce normal electrocardiograms after the administration of atropine.

Earlier publications also mention isolated cases of this anomaly (WILSON, 1915; WEDD, 1921; BAIN & HAMILTON, 1926; BACH, 1929; HAMBURGER, 1929), but the uniform nature of the syndrome had failed to be observed. The 11 cases in

question therefore aroused great interest, new cases were soon reported by different investigators, and a review of earlier electrocardiographic material made it possible in many instances to make a diagnosis with retroactive effect.

The first cases of this anomaly described in Sweden were the 5 cases published by ÖHNELL in 1937, and in the spring of 1944 he reviewed 250 cases from the literature, 85 of these being from his own material. According to LEFESCHKIN, the syndrome occurs in 5 out of every thousand heart patients in an ambulatory clientele. It seems to occur more frequently in women than in men. COSSIO (1936) mentions the proportion 7:3, and approximately the same distribution was noted in ÖHNELL's series. The syndrome is observed in patients of all ages, although there has been no mention as yet of its occurrence in new-born infants.

As regards the *morphological aspect* of this syndrome, even the original, fundamental interpretations have proved to be illusory. By means of measurements the following features have been established. Despite the fact that the P—Q interval is shortened, the distance between the beginning of the P-wave and the peak of the R-wave is usually normal, both in regular and in abnormal heart cycles (ECKEY & SCHÄFER, 1938). Thus, the shortening of the conduction time is not of the common type.

In proportion as our knowledge regarding the appearance of the tracings has widened, our ideas concerning the pathogenesis have also had to be revised. Space does not permit even a summarized account here of the many explanatory theories which have been put forward; they already number over forty since the appearance of the first publication by WOLFF, PARKINSON and WHITE. Only the two alternatives suggested by HOLZMANN and SCHERF, in 1932, as an explanation of the underlying cause will be mentioned in this paper. Both of these theories had been touched upon earlier by FENICHEL (1931/32), and they have also been confirmed by later investigators. To begin with, HOLZMANN and SCHERF established that in the majority of patients yielding tracings of

the WPW type there is a sinus rhythm, since both the distance between the auricular complexes, and their appearance, remains completely, or almost, unchanged in electrocardiograms showing alternating WPW systoles and normal systoles. They also assumed that the excitatory impulse in the ventricles must arise abnormally early and travel along some pathway other than over the bundle of His. The possible existence of such an accessory pathway had already been described, although actual proof of its existence in Man had not then been obtained. This was the bundle connecting the right auricle and the right ventricle described by PALADINO and by KENT. It was suggested that the atypical form of the initial complexes might be the result of the abnormal site for the entry of the bundle into the ventricle, and that vagal tone might have a certain influence on the direction taken by the impulse. The shortening of the conduction time could be readily explained by the fact that the physiological retardation in the auriculoventricular bundle was eliminated.

Another explanation to account for premature activation of the ventricles suggested by HOLZMANN and SCHERF was the possible occurrence of regular extrasystoles provoked from a hypersensitive focus in the ventricle which becomes mechanically stimulated as the result of diastolic distention.

The chief reason for the large number of theories regarding the mechanism of the WPW syndrome is in all probability the lack of autopsy reports and the difficulty of reproducing the syndrome experimentally. As regards the *autopsy cases*, several reports have now been published on this aspect, two of them, described by ÖHNELL, being of particular interest. One of these cases was that of a middle-aged woman who yielded the typical electrocardiogram and suffered from severe protracted attacks of tachycardia, during one of which she expired. Post-mortem examination of the heart revealed diffuse foci of round cell infiltration which might very well have corresponded to the hyperexcitable areas suggested by HOLZMANN and SCHERF. The other case was that of a woman aged 30 who had had attacks of paroxysmal tachycardia since she

was 8 years old. Three brothers and a sister suffered from the same complaint. In this case, a muscular bridge  $\frac{1}{2}$  cm. in length and 0.3 mm. in breadth between the left auricle and ventricle was observed with the naked eye. Histological examination proved that it had the typical myocardial structure, and its end were connected with the musculature of both the auricle and the ventricle. The bundle of His was normal. Contrary to the opinion of HOLZMANN and SCHERF, ÖHNELL considers that both pathways are used.

Interesting *animal experiments* have also been carried out during the past few years. In 1941, two American investigators succeeded in directly stimulating the ventricles by amplifying the action current of the auricle, and in these experiments they were able to produce electrocardiograms similar to the WPW tracings seen in clinical practice. (BUTTERWORTH and POINDEREXTER.) Quite independently of these observations, ÖHNELL found in 1942 that by stimulating one ventricle at a given moment of time before the opening of the regular QRS complex the characteristic deformation of the latter complex is obtained. He was also able to demonstrate that the bundle of His functions normally also when the systole is of the WPW type. It is thus conceivable that the mechanism responsible for the anomaly in question is as follows: Almost before the additional excitation wave has had time to radiate out over the ventricles these become activated in the usual manner by way of the bundle of His, irrespective of whether the additional wave has passed over from the auricle across an abnormal pathway or whether it has originated in some hyperexcitable focus in the ventricles themselves. If we assume the possibility of two pathways over which the excitatory impulse may pass, we are given an opening for accounting for the attacks of tachycardia by presuming the existence of a circulatory excitation wave (DE BOER, 1927). Finally, it may be mentioned that typical WPW tracings have been observed in animal experiments in connection with experimental myocardial damage (LINDNER, 1941; KAHN & STARKENSTEIN, 1910).

Of great interest both from the theoretical and the *diagnostic* standpoints is the observation made by ÖHNELL, that in patients with the WPW syndrome the first slow rise of the R-wave is closely bound to the P-wave, which it follows when changes in the P—S time occur. When the P-wave shows a displacement to the left or the right in relation to the S-wave the additional wave is thus drawn away from, or pushed in towards, the initial complex, respectively (the concertina effect described by ÖHNELL, 1942). Finally, if the node is allowed to take over the rôle of the pacemaker (e. g. through carotid sinus pressure or intravenous administration of sympatol) the initial complex from the node will be narrow. This feature accords well with the assumption that a premature activation of the ventricle is in question. If the physiological retardation in the auriculoventricular bundle is prolonged, the additional excitatory impulse ought, in fact, to have time to spread out over a larger area before it meets the regular wave, and this is what actually happens. On the other hand, if the pause in the a.-v. bundle is shortened the opposite effect is obtained instead.

The term WPW syndrome (ÖHNELL, 1940) was originally suggested as a temporary name to be used until the real nature of the anomaly was established.

The essential features with regard to its mode of origin can now be said to have been cleared up; in other words, that it is a matter of an activation connected with the auricle, arising prematurely somewhere in the ventricular part of the heart. It has therefore been suggested that the syndrome should be re-named, and the term pre-excitation has been introduced by ÖHNELL. There is also another good reason for the change of name. A group of electrocardiographic abnormalities, in all probability of some size, has been encountered in which the genesis is apparently the same although the tracings show certain divergences from those occurring in the WPW syndrome.

It must be said that, before the time of WOLFF, PARKINSON and WHITE's publication in 1930, no particular attention had

been paid to the abnormally short conduction time, especially when one makes a comparison with all the work laid down in the attempt to elucidate the clinical significance of the prolonged conduction time. Since the appearance of WOLFF, PARKINSON and WHITE's paper, however, interest in the abnormally short conduction time has increased. In HOLZMANN and SCHERF's article (1932), two cases of a new type of shortened conduction time are described. These were cases showing abrupt shortening of the conduction time without a corresponding change in the initial complexes. Other authors soon observed that in patients with the typical WPW syndrome a short conduction time is sometimes retained even after the QRS complexes have been normalized. (TUNG, 1936; KATZ & KAPLAN, 1938; and others.)

CLERC, ROBERT-LÉVY, and CRISTESCO, in 1938, reviewed 21 cases with short conduction times and normal ventricular complexes, from a series comprising several thousands of electrocardiograms. Among these patients there were 3 who had previously had attacks of paroxysmal tachycardia. The whole group, which must, however, be regarded as rather heterogeneous (cf. SÖDERSTRÖM: *Cardiologia*, 1943), was classed as a subdivision (Type 2) of the WPW syndrome (Type 1), and was assumed to have the same mode of origin. No proof of the relationship was adduced, however.

Investigations carried out on the relatives of patients yielding WPW electrocardiograms have also furnished exceedingly interesting results (ÖHNELL, 1941). Several of these relatives, both brothers or sisters of the patients and those of earlier generations, stated that they had had attacks of heart palpitations and their electrocardiograms showed deformations sufficiently characteristic to enable them to be roughly classified into certain main types.

In his thesis of 1944, ÖHNELL distinguished nine different types in addition to the WPW syndrome, on the basis of the differences in the PQ (his type C with the P—Q longer than 0.12 is of special interest here) and QRS intervals, the QRS amplitude, and the initial slope in QRS. Further evidence in



support of the theory that these electrocardiographic types are closely related to the WPW syndrome and are due to the same mechanism is the fact that they were found to alternate with WPW systoles in the same case, and that normal complexes in WPW cases could be changed into complexes belonging to one or other of these types through a change in the vegetative tone of the heart (e.g. by carotid sinus pressure), and also that the concerting effect could be demonstrated in these cases.

It has been found that there are transition forms between these types, an observation which has also been demonstrated experimentally. FELDMANN and KOCH have produced them with epinephrine, and they have also been obtained in connection with demonstrations of the concertina effect. It is thus the manner in which the two competitive impulses divide up between them the area of excitability in the ventricles that determines the appearance of the initial complex.

A diagnosis of pre-excitation can only be made by electrocardiography. The appearance of the standard tracing in itself makes a diagnosis possible and it can also arouse suspicions in the same direction. Finally, the anamnesis (attacks of paroxysmal tachycardia, cases of pre-excitation in the same family) may also serve as a guide, despite the fact that the standard tracing is completely normal.

In the following description by ÖHNELL (1944) an attempt is made to collect as many characteristics as possible which can serve as indications that pre-excitation is present.

1. Positive  $P_I$  and  $P_{II}$ .
2. P—Q interval maximum 0.12 sec.
3. QRS interval exceeding 0.10 sec.
4. QRS begins with a fairly straight curve segment with a slope of between 3 and 8 mV/Sec. in at least two extremity leads.
5. The duration of this segment is minimum 0.05 sec.
6. The amplitude of QRS, in either direction from zero-line, exceeds 0.08 mV in at least one lead.
7. The complexes recur in a number of beats, the shape remaining constant.

These features apply to adults. When it is a matter of children, the physiologically shorter conduction time must be taken into consideration.



If the patient's standard tracing or the anamnesis gives rise to the suspicion that pre-excitation is present, but it is not possible to make a sure diagnosis, there are a number of ways of making more sure of it. The chest lead is a valuable diagnostic aid, because the slow initial slope is usually most marked in this lead (ÖHNELL, 1944).

Attempts can be made to alter the interval between the two ventricular excitations and thus produce a concertina effect, and finally one can endeavour to normalize the tracings by physical exertion, by inhalation of amyl nitrite, or atropine or quinidine medication. ÖHNELL obtained normal tracings also in a few cases when the patient stood up, a finding which complements his observation that a large stroke volume in normalized cases can provoke pre-excitation. The normalization can occur instantaneously or by degrees. There is also a form of pseudo-normalization in which pre-excitation is still present although it is no longer reflected to any extent in the electrocardiogram.

WOLFF, PARKINSON and WHITE stated in 1930 that the syndrome had been encountered in individuals who were otherwise healthy and in most cases young.

The large majority of authors believe that the anomaly is of little significance and that it makes no difference to the prognosis, as far as life is concerned, even when there is concurrent heart disease. From the point of view of the prognosis, pre-excitation has been compared to paroxysmal tachycardia, which also occurs most commonly in young and otherwise healthy individuals. Some of these cases have another heart complaint also which possibly might be causally related to the disturbance under discussion. In these cases also, deaths occur in connection with paroxysmal attacks which, when they occur frequently, put a heavy strain on the heart.

This view, viz. that pre-excitation is practically without significance has undergone certain modifications during the past few years. HUNTER, PAPP and PARKINSON have stated that among 90 cases they had reviewed, 18 showed signs of heart disease (e. g. hypertonia, or valvular or coronary diseases), and

that in at least 6 of these there was strong reason to suspect an acquired etiological factor; in other words, a causal connection between the heart disease and the syndrome. (Appearing, for instance, in connection with the first attack of a rheumatic carditis, after a thyrotoxic crisis or a fresh coronary thrombosis.)

The prognosis as far as health is concerned is governed by the type of mechanism which lies at the root of the abnormality. If it is a question of an abnormal muscular connection the conducting capacity of this muscular bridge will be the deciding factor. If, on the other hand, the syndrome is produced by a hyperexcitable focus in the ventricular part of the heart then the prognosis will be governed by whether the excitability of this focus has a tendency to be reduced. Many cases have been observed in which the condition was still unchanged after a period of 10—15 years. There are reports of cases where normalization occurred after such interventions as thyroidectomy (LAMB, 1933), and tonsillectomy (MACHOLD, 1938). Reports on other types of therapeutic observations are meagre. There has not yet been time to gather experience on this aspect. Possibly it is worth mentioning here that quinidine seems to produce normalization in some cases.

Pre-excitation is a not uncommon abnormality, and as it reveals itself in widely differing shapes, it has an interest from the practical clinical point of view. It not infrequently happens that this condition is wrongly interpreted as severe heart disease, with serious consequences for the patient's mode of living. Owing to its connection with paroxysmal tachycardia and auricular fibrillation it is closely allied to problems of vital interest in the field of electrocardiographic research.

Two cases of pre-excitation which were treated at the Norrtull Hospital for Children in 1942 and which demonstrate clearly the great morphological variety occurring in connection with this abnormality are described in this paper.

I also append a review in tabular form<sup>1</sup> of the cases of

<sup>1</sup> The interpreting of the electrocardiograms and the constructing of

*Table.*

Author	Age in years. Sex	Paroxysmal tachycardia	Observations
CLERC & collaborators, 1938	15 ♂	+	Previous rheumatic manifestations. Examination of heart: Faint systolic murmur over apex, otherwise nothing abnormal
ÖHNELL, 1944	15 ♂	+	
WOLFERTH & WOOD, 1933	14 ♀	+	Attacks of paroxysmal tachycardia about once a week since age of 2. Examination of heart: Except for electrocardiogram, nothing abnormal
	14 ♂	}	Discovered at routine-examination. No other signs of heart disease. Radiogram of heart normal
	13 ♂		
COSSIO & collaborators, 1935/36	14 ♀	—	Examination of heart: Slight systolic murmur. Radiogram of heart normal
WOOD, WOLFERTH, & GECKELER, 1943	14 ♂	+	Patient died after an attack of tachycardia 2 years after first attack. No previous signs of heart disease
KISS, 1941	14 ♂		Heart pains since age of 3, after diphtheria. No other signs of heart disease. Radiogram of heart negative
TESCHENDORF, 1939	14 ♀	—	Diphtheria in anamnesis. Examination of heart, with radiogram: Normal
LEVINE & BEESON, 1941	13 ♂	+	Previously healthy. No infections injurious to the heart. Examination of heart, with radiogram: Normal
BISHOP, 1937	13 ♂	+	Examination of heart: Normal
WOLFF, PARKINSON & WHITE, 1930	11 ♂		Paroxysmal bradycardia. Patient easily fatigued for past few years. Went in for sport, however
ÖHNELL, 1944	11 ♂	+	Enlargement of heart. Congenital vitium cordis? Under observation for 8 years
	10 ♂	—	Discovered at routine examination. Examination of heart: Normality

Author	Age in years. Sex	Paroxysmal tachycardia	Observations
BAIN & HAMILTON, 1926	10 ♂	—	Rheumatic carditis for 1 month. Heart slightly enlarged but no signs of endocarditis
FELDMANN, 1942	10 ♀		
BUTTERWORTH & POIN- DEREXTER, 1942	9 ♀	+	No other signs of heart disease. Electrocardiogram unchanged during 15 years' observation
AASTRUP, 1937	7 ♂		Feverish, with arthralgia and a swollen joint 5 weeks before electrocardiographic examination
ZARDAY, 1937	7		
PETER, 1943	6 ♂		Diphtheria and endocarditis. About 1 month later, sepsis lenta. Death
HUNTER, PAPP & PARKINSON, 1941	6	—	WPW syndrome appeared directly after an attack of rheumatic fever, which had no other effect on the heart
KISS, 1941	6 ♂	+	Previously healthy. Only an angina in anamnesis. Harsh systolic murmur over heart. Radiogram of heart normal. Diagnosis: Asthma + congenital vitium cordis
NÁDRAI, 1941	6 ♂		The typical electrocardiogram appeared after an attack of enteritis with fever. (Dysentery?)
COSSIO et al, 1935/36	4 ♂		
HAMBURGER, 1929/30	4 ♂		During the attacks the heart beat rose to as much as 240
ÖHNELL, 1941	2 ♂		Several cases of pre-excitation in family. Radiographic examination of heart: Enlargement. Congenital vitium cordis?
NÁDRAI, 1941. (This author mentions 4 more cases, 3 in connection with infectious diseases, but gives no further information about them)	3 weeks ♂		Globular heart + ranula. The case was followed for 4 years. Developed normally

pre-excitation in children hitherto mentioned in the literature.

All in all, the literature contains mention of 31 children, but all information is lacking with regard to 4 of them. Paroxysmal tachycardia is mentioned in 10 instances. Four of the children showed signs of congenital vitium cordis. It is of interest to note that POHLMAN, in 1941/42, mentioned 2 cases (adult patients) displaying the combination congenital heart defect and pre-excitation.

As typical examples of the two assumed modes of origin we can take — for the acquired type — one of the cases mentioned by NÁDRAI, in which the patient to begin with had a normal electrocardiogram which changed into the characteristic pre-excitation tracings in connection with an attack of enteritis with fever, or, in the words of NÁDRAI: »Entwickelt sich vor unseren Augen». The congenital type is represented by one of the cases of WOOD and his collaborators. At the post-mortem examination in this case numerous muscular bridges between the right auricle and ventricle were observed. In this connection it can be mentioned that a case with a seriously malformed heart was described by MÖNCKEBERG in 1913. An additional connection between the auricle and the ventricle, anastomosing with the regular activation system, was observed at autopsy. The case was that of a child aged 6 years. An electrocardiographic examination does not seem to have been carried out.

### Case reports.<sup>1</sup>

*Case 1.* A boy aged 13 who was under observation in hospital for his mental condition. (He had difficulty in keeping up with the work in an auxiliary class.) Nothing of interest in the family history. He had always been healthy, apart from an attack of pneumonia at the age of 2. During the past year he had had un-

the table were done in collaboration with Dr. R. ÖHNELL, to whom I take this opportunity of proffering my grateful thanks for his assistance.

<sup>1</sup> Both have been described briefly in another connection. (*Cardiologia* fasc. 3/4 193:1943.)

accountable attacks of heart palpitations. He had several times called out to his mother and asked her to feel how fast his heart was beating. »Now it is really hopping!» The only positive finding from the physical examination was a short, soft systolic murmur over the whole heart and a slightly sharp first tone. Electrocardiogram: P—Q time 0.10 sec., QRS interval 0.12 sec. The QRS complex was deformed by a small notch at the base in leads II and III which could easily have been overlooked, and the tracing bore a strong resemblance to a normal electrocardiogram. Normalization was not obtained with atropine or after physical exertion. The concertina effect could be demonstrated, however, by intravenous injection of sympatol. After this measure a nodal rhythm could be observed here and there, and at the points of transition sinus rhythm interfered. A number of complexes obtained after experiments of the kind mentioned are shown in figure 1.

The first complex (a 1) is nodal, and it will be observed that the characteristic slow initial rise in QRS of the standard tracing (1 e) is totally absent. In 1 b the P-wave can be seen, in this tracing lying close to the QRS complex. In 1 c, following the P-wave,

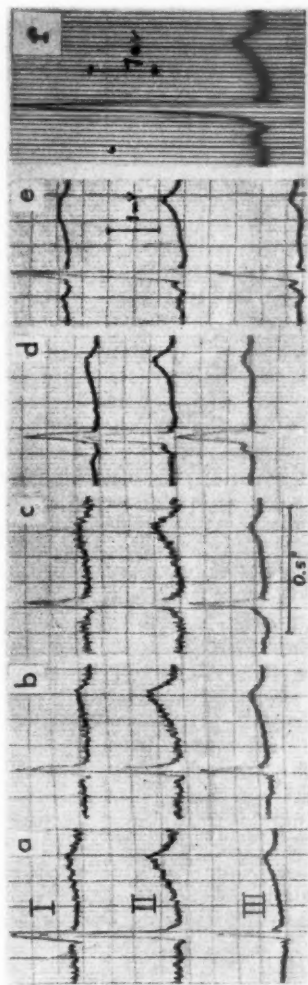


Fig. 1. Case 1. a—d = electrocardiographic complexes from an experiment with sympatol, administered intravenously. (See text.) Complex e = the patient's normal tracing. f = chest lead (from the apex region to the right arm).

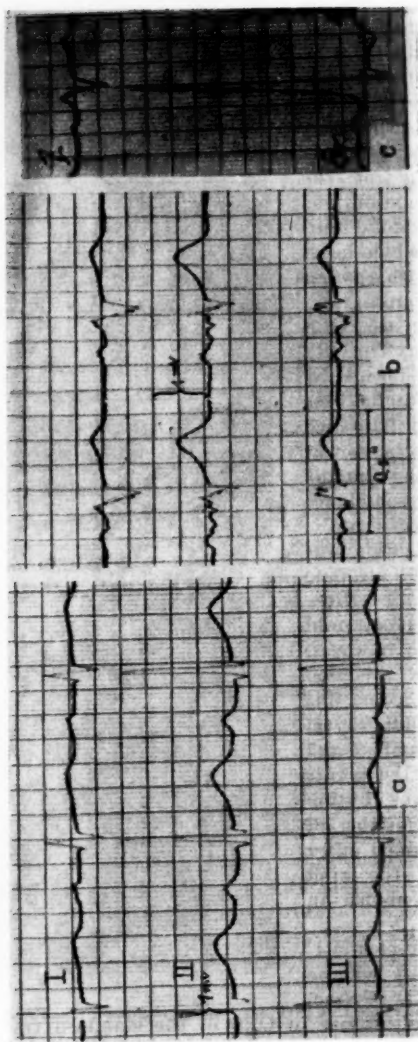


Fig. 2. a = electrocardiogram after administration of quinidine. b = the patient's normal tracing. c = chest lead.

there is a slowly rising segment at the base of the R-wave, most clearly distinguishable in lead III. In the next complex, the P-wave has moved still further towards the left (in relation to the end of the QRS complex) and the slowly rising segment is now slightly longer.

*Case 2.* A girl aged 13, hospitalized under a diagnosis of severe myocarditis. The child had been born at home, 5 weeks before term. At the age of 3 weeks she had had convulsive attacks. Her static and psychic development were delayed. At the time of her birth one of her eyes was found to be defective and in 1941 she was operated upon for a cataract in the right eye. In 1940 she became stone-deaf within the course of a few days. According to a specialist, this was due to brain damage. She was sent to a deaf-and-dumb school and placed in an auxiliary class. She has always had a tendency to suffer from breathlessness, but there have been no other symptoms from incomensation. During the weeks before her admission to the hospital she had had repeated attacks of palpitation and pains around the heart. An electrocardiogram was taken and the patient was hospitalized. Examination of the heart revealed a fairly soft systolic murmur most pronounced in the third intercostal space to the left, close to the sternum. The blood pressure and the radiogram of the heart were normal. Wassermann reaction negative. S. R., 7 mm. The electrocardiogram showed a conduction time of 0.10 sec. Contrary to the findings in all of WOLFF, PARKINSON and WHITE's cases the QRS complexes in all leads in this case were relatively low (in other tracings from the same case the largest amplitude was 0.5 mV). There was some justification therefore for suspecting that an arborization block was in question. The proof that this tracing was also to be regarded as an example of the WPW anomaly lay in the fact that it could be normalized so as to give the same P—S time as in the standard tracing. This is one of the classical characteristics of the WPW cases. The normalization was produced in this case with quinidine. Apart from the slightly prolonged a.-v. time, the quinidine tracing (fig. 2 a) contains no abnormal features. The change-over from 2 a to 2 b could be repeated as often as desired.

### Summary.

The author gives a brief description of the term pre-excitation, one of the points emphasized being the great morpho-



logical diversity shown by the electrocardiograms. Two case reports are appended. All the previously published cases of pre-excitation in children are presented in tabular form.

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## **A hospital epidemic of chickenpox.**

By

**BIRGER JÖNSSON.**

As is well-known, chickenpox is as a rule a benignant disease, which appears without complications and which offers little of interest clinically. The epidemic to be described here from the viewpoint of epidemiology is nevertheless of interest, since it throws light on the way in which the disease spreads. The cases occurred in Eskilstuna Infectious-Diseases Hospital; in other words, we are concerned with material which had been under careful observation from the start.

At the time the epidemic appeared, there were no known cases of the disease in town. The infection was transferred to the Infectious-Diseases Hospital there via a scarlatina case, which had earlier on been treated at one of the other Infectious-Diseases Hospital of the District (»län»), but which had been referred to the one at Eskilstuna on account of ear complication, which called for care of a specialist. There had been chickenpox at the first-named hospital during the last few months, but as the patient had been treated there for about 5 weeks without contracting it, there did not seem to be any risk of his being in the incubation stage. Despite this, he was for the first week isolated in the observation department of the Eskilstuna Hospital, after which he was transferred to the scarlatina department, owing to lack of space, on 20/9. On 26/9 the patient contracted chickenpox.

At the latter date, 57 cases of scarlatina were being treated in the department ( $S_1 + S_2$ ). It was immediately shut off, the patients' contact with the outer world being subsequently confined wholly to the staff. Of the 57 cases, 29 had had chicken-

pox, 23 contracted it, and 5 — who, according to their own report, had not had the disease — did not contract it. The infection spread subsequently to 4 other departments. As soon as it appeared the departments were shut off, to confine the infections to the patients within.

The second department ( $D_1$ ) contained 33 patients, of whom 7 had had chickenpox and 22 contracted it. 4 patients, who declared they had not had the disease, did not catch it. In the 3rd department (Pavilion), containing 40 patients, the figures were 15, 16 and 9 respectively; in the 4th department ( $S_1$ ), containing 29 patients, they were 7, 16 and 6 respectively and in the 5th ( $S_2$ ), containing 24 patients, 11, 9 and 4 respectively. Cases of chickenpox also occurred among the medical and nursing staff, which contributed to their not being able to prevent the spread of the infection from department to department.

In the accompanying diagram the departments and the cases of chickenpox which occurred have been dotted in. A glance shows that the cases appeared in groups. This can be seen most clearly at the beginning of the epidemic. The first case on  $^{26}/_9$  is followed by a group of cases 14 days later, and after about the same interval comes a fresh group. This beginning of the epidemic would seem primarily to suggest that the disease is infectious only for a comparatively short time, and that the incubation period varies only moderately. It is not known at what juncture the infection is transferred. It is both possible and probable that this juncture coincides with the first symptoms of the disease. This matter cannot be determined on the basis of the present material, however. Under all circumstances, it is reasonable to date the infectiousness from the outbreak of the disease, which course has been adopted throughout. When working out the epidemiological conditions regard must, moreover, be paid to the variability. The first case gave secondary cases after 14 days, with variability of 4—5 days. The infection of the next group can be dated from its first or its last case (or an intermediate one), which means that the mean period for incubation will now

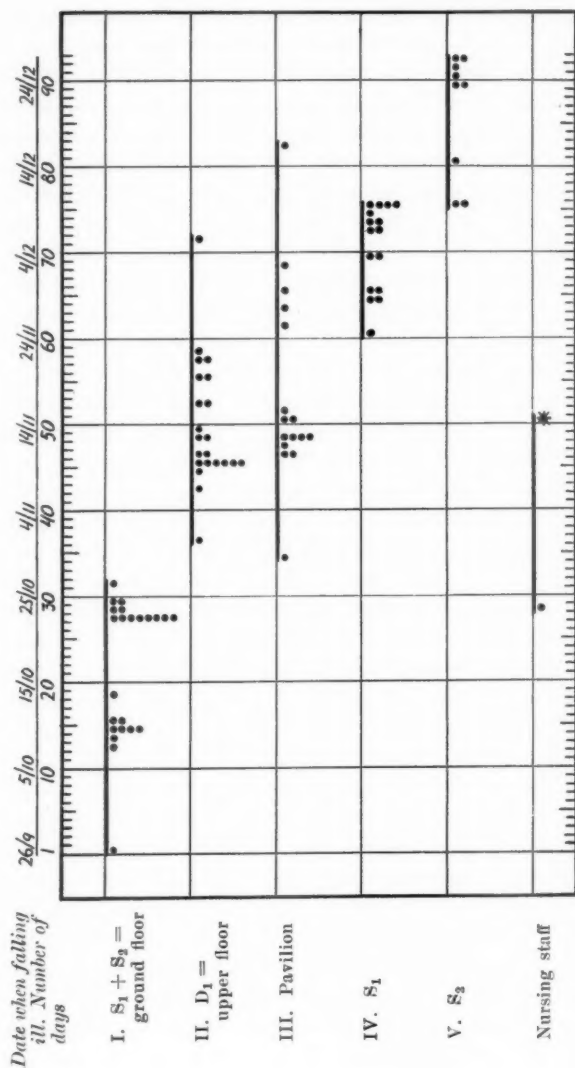


Fig. 1. Diagram giving the distribution of cases (marked as points) on the different wards (marked as lines).  $S_1$  and  $S_2$  were at first one ward which was closed; later on both were opened up as separate wards. The case marked with a star is difficult to explain.

vary. Furthermore, there will probably be a variability round these different means. The next group will be more outspread, therefore, and the same is true for the one following.

By applying the values obtained from the incubation period and its variation in the first group, it is possible to analyse the whole material; it is then not difficult to find agreement, apart from a few knotty cases which can nevertheless be fitted into the mechanism with the help of assumed transference of infection between departments. One single case does not tally, however. The result is interesting, since it at all events proves that the disease is infectious for a very short time only. The circumstance has probably not been noticed before, due to the fact that it can only be shown under exceptionally favorable conditions.

Another interesting circumstance is that, in spite of the extensive receptivity (lowered powers of resistance), those exposed to infection do not contract the disease at the same time. Though highly liable, a number of patients escape the first infection, though they are not immune, since they contract the disease during a later spread. An attempt has been made to determine those who are receptive on the basis of those who had not had the disease earlier on. It was found that 69 had done so, and that 86 contracted it; 28 did not. In other words, 84.7 % are receptive. It is possible that some of these 28 had had the disease, but so slightly that it was not observed. In a number of cases, then, there may have been acquired immunity.

As regards the spread of infection, it can be seen that a case carrying infection for a short period need not always infect those in the immediate vicinity; the disease may penetrate to the far ends of the wards, passing over receptive individuals who do not contract it until a later occasion. Two possibilities then present themselves. One is that the receptivity varies from one point in time to another. Some persons in the vicinity of the infection may, during the short time it is being spread, have an unreceptive phase just then, but be receptive at a later spread. The other is that the infection

attacks a receptive individual with a certain frequency, depending not on a general immunity in the patient in question but on local conditions in mucosae, etc. A certain minimum of virus spread through the air may be necessary before the effect can be reached. Factors of these kinds may contribute to a chance result, i. e. cause a certain number to be infected and a certain number to escape. If this is the process, an epidemic should go through a material and attack more and more receptive persons, nevertheless always leaving some who escape. The epidemic will then end without attacking all receptive cases to 100 %. No definite conclusions can be drawn as regards this theoretical possibility.

Under all circumstances, the practically important result remains that not everyone exposed to infection contracts the disease, and that the disease proceeds in stages even when the possibilities of infection are good.

## **Veränderungen des weissen Blutbildes und der Erythrozyten-Werte beim Säugling durch künstlich erzeugtes kurzdauerndes Fieber.**

Von

**ELISABETH MAASIK.**

Die nachstehenden Versuche sind an Säuglingen und an einem Kleinkinde ausgeführt worden.

Die Anschauungen der verschiedenen Autoren über Veränderungen sowohl des leukozytären wie auch des erythrozytären Blutbildes bei verschiedenen Reizen sind sehr zahlreich, in gewissen Punkten stehen sie sogar im Gegensatz zueinander. Schon die Angaben über die Normalwerte der Blutformel weisen grosse Unterschiede auf.

Die hämapoetischen Apparate reagieren beim jungen Kinde mehr auf Einflüsse aller Art; feine Reize können schon erhebliche Änderungen der Blutformel verursachen (Benjamin).

Da beim Säugling und Kleinkind keine geschlechtlichen Unterschiede des Blutbildes nachweisbar sind (Opitz), habe ich die Versuche sowohl bei Knaben als auch bei Mädchen ausgeführt.

Über Veränderungen des Blutbildes bei infektiösen Prozessen sind zahlreiche Arbeiten veröffentlicht worden, vor allen Dingen von SCHILLING. SCHILLING teilt die Veränderungen des Differentialblutbildes in 3 Phasen ein: 1. Die neutrophile Kampfphase — Linksverschiebung. 2. Die monozytäre Abwehr- und Überwindungsphase. 3. Die lymphozytäre Heilphase. Die 1. Phase geht meistens mit einer Leukozytose einher, die in der 3. Phase zurückgeht. Eine gewisse Ähnlichkeit mit dieser Gesetzmässigkeit habe ich beim künstlich erzeugten Fieber,

bei dem es sich zwar nur um eine Fieberperiode von einigen Stunden handelt, feststellen können. Schillings Beobachtungen sind bei mehrtägigem Fieber gemacht worden.

EHRlich spricht von einer Neutrophilie mit Lymphozytopenie, mit meistens gleichzeitiger Vermehrung der Gesamtmenge der weissen Blutkörper, beim Fieber. SCHILLING behauptet, dass die Lymphozytopenie als ein natürliches relatives Begleitsymptom bei der Neutrophilie anzusehen ist. HOFF spricht von einer Leukozytose durch künstliche Hyperthermie. Im Jahre 1932 haben KIJANEN und HIETARINTA eine Arbeit über Wärmeregulierung und Leukozytose in warmen Bädern veröffentlicht. Sie haben festgestellt, dass warme Bäder beim Säugling Fieber mit in fast allen Fällen gleichzeitiger Leukozytose hervorrufen.

Bei meinen Versuchen habe ich zur Erzeugung von Fieber heisse Bäder, Vollmilchinjektionen, Pyrifer- und Pyrisaninjektionen vorgenommen. Das Alter der Patienten schwankte zwischen 2—13 Monaten. Sämtliche Versuche sind in der Zeit vom 12. 6. 44—9. 9. 44 ausgeführt worden. Zur näheren Erläuterung der gefunden Ergebnisse folgen hiermit die Berichte über einige Versuche.

#### Fieber hervorgerufen durch heisse Bäder.

##### 1. Versuch.

12. 6. 44. Pat. Y—P. ♂ Nr. 395. Geb. am 9. 4. 44. Geburtsgewicht 2790 g.

Diagn. Paresis recti et vesicae urinae. Anomaliae cong. extrem. sup. et inf.

Status praesens: Allgemeinzustand zufriedenstellend.

App. resp.: 0, App. circ.: 0, App. digest.: 0.

Vor dem Versuch:

Temp. 36,1

Blutbild: Leukozyten (L) 6200, Erythrozyten (E) 3170000.

Differentialblutbild:

Basophile (Bas.) . . . . .	—	Stabkernige (St.) . . . . .	7
Eosinophile (Eos.) . . . . .	2	Segmentkernige (Sg.) . . . . .	42
Myelozyten (Myel.) . . . . .	—	Lymphozyten (Ly.) . . . . .	48
Jugendliche (Jg.) . . . . .	—	Monozyten (Mon.) . . . . .	2

Neutroph. 49 %.



## Ausführung des Versuches:

15 Min. heisses Vollbad 41,5

Sofort nach dem Bade:

Temp. 39,5

Blutbild: L. 16250, E. 3050000.

## Differentialblutbild:

Bas.	Eos.	Myel.	Jg.	St.	Sg.	Ly.	Mon.
1,5	1	—	3,5	8,5	53	30,5	2,5

Neutroph. 65 %

## 1 Stunde nach dem Bade:

Temp. 36,9

Blutbild: L. 10000, E. 3390000.

## Differentialblutbild:

Bas.	Eos.	Myel.	Jg.	St.	Sg.	Ly.	Mon.
—	—	—	—	7	39	53	1

Neutroph. 47 %

## 3. Versuch.

14. 6. 44. Pat. Y—P. ♂ Nr. 395. (Nähere Angaben siehe Versuch Nr. 1.)

Status praesens: Allgemeinbefinden zufriedenstellend.

App. resp.: 0, App. circ.: 0, App. digest.: 0.

Vor dem Versuch:

Temp. 36,4

Blutbild: L. 6100, E. 3680000.

## Differentialblutbild:

Bas.	Eos.	Myel.	Jg.	St.	Sg.	Ly.	Mon.
4	2	—	—	5	45	44	—

Neutroph. 50 %.

## Ausführung des Versuches:

15 Min. heisses Vollbad 41

Sofort nach dem Bade:

Temp. 38,8

Blutbild: L. 11400, E. 2800000.

## Differentialblutbild:

Bas.	Eos.	Myel.	Jg.	St.	Sg.	Ly.	Mon.
—	1	—	—	3	43	49	4

Neutroph. 46 %.

## 1 Stunde nach dem Bade:

Temp. 36,6

Blutbild: L. 11600, E. 3210000.

## Differentialblutbild:

Bas.	Eos.	Myel.	Jg.	St.	Sg.	Ly.	Mon.
3	5	—	1	7	47	29	8

Neutroph. 55 %.

## 9. Versuch.

4. 8. 44. Pat. P. U. ♂ Nr. 530. Geb. am 26. 1. 44. Diagn. Hydrocephalus.  
Status praesens: Allgemeinzustand befriedigend.

App. resp.: 0, App. circ.: 0, App. digest.: 0.

Ausführung des Versuches:

12 Min. heisses Vollbad 40—43.

Vor dem Versuch:

Temp. 37,5

Blutbild: L. 7000, E. 4820000.

Differentialblutbild:

Bas.	Eos.	Myel.	Jg.	St.	Sg.	Ly.	Mon.
1	1	2	—	4	29	53	10

Neutroph. 33 %.

Sofort nach dem Bade:

Temp. 38,7

Blutbild: L. 7700, E. 4310000.

Differentialblutbild:

Bas.	Eos.	Myel.	Jg.	St.	Sg.	Ly.	Mon.
1	—	2	—	5	36	45	11

Neutroph. 41 %.

1 Stunde nach dem Bade:

Temp. 37,3

Blutbild: L. 5700, E. 4680000.

Differentialblutbild:

Bas.	Eos.	Myel.	Jg.	St.	Sg.	Ly.	Mon.
1	1	1	—	5	30	52	10

Neutroph. 35 %.

Beim Vergleich der gefundenen Werte bei den 9 ersten Versuchen, von welchen ich hier nur die obigen Beispiele anführe, die an 5 verschiedenen Patienten vorgenommen sind, bei denen das Fieber durch heisse Bäder erzeugt wurde, sehen wir bei allen ein *Steigen der Leukozytenwerte*, zwar nicht bei allen in grossem Masse. Gleichzeitig sehen wir bei allen ein *Sinken der Erythrozytenwerte*. Im Differentialblutbild sehen wir bei fast allen Fällen eine *deutliche Linksverschiebung*. Besonders die Anzahl der neutrophilen Segmentierten ist, wie wir sehen, besonders grossen Veränderungen unterworfen. In fast allen Fällen sehen wir gleichzeitig ein *Absinken der Lymphozytenwerte*.

Interessant ist die Tatsache, dass beim Blutbilde 1 Stunde

nach dem Bade die Erythrozyten annähernd ihre Ausgangswerte (vor dem Versuch) erreicht haben. Auch die Leukozytenzahl ist in den meisten Fällen im Absinken.

Die Werte der Neutrophilen sind fast die gleichen wie ihre Ausgangswerte.

In den Werten der Lymphozyten finden wir auch ein Annähern an die Ausgangswerte.

Am deutlichsten sind die Unterschiede der Erythrozyten- und Leukozytenwerte, wir können hier eine gewisse *Gesetzmässigkeit* beobachten.

#### Fieber hervorgerufen durch Vollmilchinjektionen.

##### 11. Versuch.

19. 6. 44. Pat. Y.—P. ♂ Nr. 395. (Nähere Angaben siehe Versuch Nr. 1.)

Status praesens: Allgemeinzustand zufriedenstellend.

App. resp.: 0, App. circ.: 0, App. digest.: 0.

Ausführung des Versuches:

1 cem gekochte Vollmilch intramusc.

Vor der Injektion:

Temp. 36,6

Blutbild: L. 6400, E. 3030000

Differentialblutbild:

Bas.	Eos.	Myel.	Jg.	St.	Sg.	Ly.	Mon.
2	6	1	—	9	33	38	10

Neutroph. 42 %.

1½ Stunden nach der Injektion Temp. 36,5.

7 Stunden nach der Injektion:

Temp. 37,7

Blutbild: L. 8300, E. 2800000.

Differentialblutbild:

Bas.	Eos.	Myel.	Jg.	St.	Sg.	Ly.	Mon.
1	4	—	—	7	47	35	8

Neutroph. 54 %.

##### 13. Versuch.

7. 7. 44. Pat. U. A. ♀ Nr. 489. Geb. am 18. 1. 44. Diagn. Morbus Little.

Status praesens: Allgemeinzustand befriedigend.

App. resp.: 0, App. circ.: 0, App. digest.: 0.

Ausführung des Versuches:

2 cem gekochte Vollmilch intramusc.

Vor der Injektion:

Temp. 36,9

Blutbild: L. 6800, E. 4020000.

Differentialblutbild:

Bas.	Eos.	Myel.	Jg.	St.	Sg.	Ly.	Mon.
—	—	—	—	5	44	47	4

Neutroph. 49 %.

2 1/2 Stunden nach der Injektion:

Temp. 37,9

Blutbild: L. 4500, E. 3216000.

Differentialblutbild:

Bas.	Eos.	Myel.	Jg.	St.	Sg.	Ly.	Mon.
1	3	—	—	1	36	52	8

Neutroph. 37 %.

6 1/2 Stunden nach der Injektion:

Temp. 39,7

Blutbild: L. 8500, E. 3270000.

Differentialblutbild:

Bas.	Eos.	Myel.	Jg.	St.	Sg.	Ly.	Mon.
1	4	—	—	5	63	24	9

Neutroph. 68 %.

21 Stunden nach der Injektion:

Temp. 37,1

Blutbild: L. 8600, E. 4020000.

Differentialblutbild:

Bas.	Eos.	Myel.	Jg.	St.	Sg.	Ly.	Mon.
2	—	—	—	4	34	51	11

Neutroph. 38 %.

Die Versuche mit Vollmilchinjektionen erstrecken sich im einzelnen Versuch auf eine längere Zeitspanne. In den meisten Fällen bekommt der Patient erst nach 3—7 Stunden Fieber. Bei einigen Fällen, bei denen die Temperaturerhöhung sehr gering ist, weist das Differentialblutbild kaum Veränderungen auf, wir sehen jedoch ein *geringes Ansteigen der Leukozytenwerte*. Man erhält jedoch den Eindruck, dass die Erythrozytenwerte am empfindlichsten reagieren, denn in allen Fällen sehen wir ein *deutliches Absinken der Erythrozytenwerte*. Beim Versuch 13 sehen wir ein deutlicheres Ansteigen der Temperatur und dementsprechend deutlichere Veränderungen der Blutformel, ähnlich den Veränderungen beim Fieber durch heisse Bäder.

**Fieber hervorgerufen durch Pyrifer und Pyrisan.***15. Versuch.*

5. 7. 44. Pat. U. A. ♀ Nr. 489. (Nähere Angaben siehe Versuch Nr. 13.)

Status praesens: Allgemeinzustand befriedigend.

App. resp.: 0, App. circ.: 0, App. digest.: 0.

Ausführung des Versuches:

250. E. Pyrifer intramusc.

Vor der Injektion:

Temp. 36,9

Blutbild: L. 6900, E. 4070000.

Differentialblutbild:

Bas.	Eos.	Myel.	Jg.	St.	Sg.	Ly.	Mon.
—	1	—	—	8	34	56	4

Neutroph. 42 %.

6 Stunden nach der Injektion.

Temp. 37,9

Blutbild: L. 9500, E. 3790000.

Differentialblutbild:

Bas.	Eos.	Myel.	Jg.	St.	Sg.	Ly.	Mon.
1	1	—	—	2	51	40	4

Neutroph. 53 %.

22 Stunden nach der Injektion:

Temp. 37,1

Blutbild: L. 6800, E. 4020000.

Differentialblutbild:

Bas.	Eos.	Myel.	Jg.	St.	Sg.	Ly.	Mon.
—	—	—	—	5	44	51	—

Neutroph. 49 %.

*16. Versuch.*

10. 7. 44. Pat. U. A. ♀ Nr. 489. (Nähere Angaben siehe Versuch Nr. 13.)

Status praesens: Allgemeinzustand befriedigend.

App. resp.: 0, App. circ.: 0, App. Digest.: 0.

Ausführung des Versuches:

25 E. Pyrifer intraven.

Vor der Injektion:

Temp. 36,8

Blutbild: L. 6300, E. 3960000.

Differentialblutbild:

Bas.	Eos.	Myel.	Jg.	St.	Sg.	Ly.	Mon.
—	2	—	—	4	25	58	11

Neutroph. 29 %.

5½ Stunden nach der Injektion:

Temp. 39,0

Blutbild: L. 7500, E. 3840000.

Differentialblutbild:

Bas.	Eos.	Myel.	Jg.	St.	Sg.	Ly.	Mon.
—	3	—	1	3	50	40	3

Neutroph. 54 %.

9 Stunden nach der Injektion:

Temp. 36,9

Blutbild: L. 8500, E. 3950000.

Differentialblutbild:

Bas.	Eos.	Myel.	Jg.	St.	Sg.	Ly.	Mon.
1	1	—	—	4	43	44	7

Neutroph. 47 %.

18. Versuch.

2. 9. 44. Pat. H. H. ♀ Nr. 506. Geb. am 3. 6. 43. Diagn. Gas troenteritis chron.

Aufnahme ins Krankenhaus am 12. 7. 44.

Status praesens: Allgemeinzustand befriedigend.

App. resp.: 0, App. circ.: 0, App. digest.: 0.

Ausführung des Versuches:

Pyrisan (Orion) intraven. 1 cem.

Vor der Injektion:

Temp. 36,4

Blutbild: L. 14000, E. 4080000.

Differentialblutbild:

Bas.	Eos.	Myel.	Jg.	St.	Sg.	Ly.	Mon.
2	1	—	—	2	32	54	8

Neutroph. 34 %.

3 Stunden nach der Injektion: Temp. 37,2, Pat. weinerlich, etwas unruhig.

3 Stunden 20 Min. nach der Injektion: Schüttelfrost, Temp. 37,6

4 Stunden 30 Min. nach der Injektion:

Temp. 39,9

Blutbild: L. 17000, E. 3990000.

Differentialblutbild:

Bas.	Eos.	Myel.	Jg.	St.	Sg.	Ly.	Mon.
1	1	—	—	3	52	35	8

Neutroph. 55 %.

6 Stunden nach der Injektion: Kind schläft ruhig.

9 Stunden nach der Injektion:

Temp. 36,2

Blutbild: L. 18400, E. 4680000.

## Differentialblutbild:

Bas.	Eos.	Myel.	Jg.	St.	Sg.	Ly.	Mon.
—	1	—	—	—	50	46	5

Neutroph. 50 %.

## 19. Versuch.

6. 9. 44. Pat. H. H. ♀ Nr. 507. (Nähere Angaben siehe Versuch Nr. 18.)

Status praesens; Allgemeinzustand gut.

App. resp.: 0, App. circ.: 0, App. digest.: 0.

Ausführung des Versuches:

Pyrisan (Orion) intraven. 1 ccm.

Vor der Injektion:

Temp. 35,9

Blutbild: L. 13300, E. 3990000.

## Differentialblutbild:

Bas.	Eos.	Myel.	Jg.	St.	Sg.	Ly.	Mon.
—	1	—	—	4	29	61	5

Neutroph. 33 %.

2 Stunden nach der Injektion: Schüttelfrost, Vomitus.

3 Stunden 45 Min. nach der Injektion:

Temp. 40,5

Blutbild: L. 13650, E. 3780000.

## Differentialblutbild:

Bas.	Eos.	Myel.	Jg.	St.	Sg.	Ly.	Mon.
—	1	—	—	2	62	31	4

Neutroph. 64 %.

15 Stunden nach der Injektion:

Allgemeinbefinden gut.

Temp. 36,4

Blutbild: L. 23100, E' 4230000.

## Differentialblutbild:

Bas.	Eos.	Myel.	Jg.	St.	Sg.	Ly.	Mon.
—	1	—	—	2	55	38	5

Neutroph. 57 %.

## 20. Versuch.

2. 9. 44. Pat. N. E. ♂ Nr. 584. Geb. am 16. 6. 44. Diagn. Ekzema.

Status praesens: Allgemeinzustand gut.

App. resp.: 0, App. circ.: 0, App. digest.: 0.

Ausführung des Versuches:

0,6 cmm Pyrisan (Orion) intraven.

Vor der Injektion:

Temp. 36,6

Blutbild: L. 15700, E. 4740000.

## Differentialblutbild:

Bas.	Eos.	Myel.	Jg.	St.	Sg.	Ly.	Mon.
—	3	—	—	3	30	57	7

Neutroph. 33 %.

4 Stunden nach der Injektion:

Temp. 38,0

5 Stunden nach der Injektion:

Temp. 38,6

Blutbild: L. 26000, E. 3810000.

## Differentialblutbild:

Bas.	Eos.	Myel.	Jg.	St.	Sg.	Ly.	Mon.
—	3	—	—	1	53	39	5

Neutroph. 54 %.

6 St. 30 Min. nach der Injektion:

Temp. 37,1

Blutbild: L. 21000, E. 4500000.

## Differentialblutbild:

Bas.	Eos.	Myel.	Jg.	St.	Sg.	Ly.	Mon.
1	2	—	—	2	50	42	3

Neutroph. 52 %.

Obgleich Pyrifer bei 2 Fällen intramuskulär injiziert worden ist und die Temperatursteigerung gering ist, merkt man schon deutliche Veränderungen der Blutformel. Besonders auffallend ist im Differentialblutbild das *grosse Ansteigen der Neutrophilen*, wir sehen hier deutlich die von Schilling erwähnte Kampfphase (bei Infektionen). Gleichzeitig sehen wir deutliche Veränderungen der Leukozyten- und Erythrozytenwerte. Im Laufe von 24 Stunden haben die Patienten die Ausgangstemperatur mit gleichzeitigen Ausgangswerten der Erythrozyten und Leukozyten fast erreicht.

Bei den intravenösen Pyrisan-Injektionen sehen wir, dass die Werte der Neutrophilen nach 24 Stunden noch hoch sind, die Leukozyten- und Erythrozytenveränderungen gleichen denen bei den intramuskulären Injektionen.

Bei den Injektionen des einheimischen Präparates Pyrisan (*Bact. faecalis alcaligenes*) sehen wir ähnliche Werte wie bei den Versuchen mit Pyrisan, auch das Einsetzen des Fiebers findet hier nach der gleichen Zeitspanne statt.



Obgleich die Anzahl der ausgeführten Versuche gering ist, können wir, wenn wir die Ergebnisse der einzelnen Versuche vergleichen, doch eine gewisse Gesetzmässigkeit finden. Interessant ist die Tatsache, dass das kindliche Blut bei so kurzdauernden Fieberperioden (in den meisten Fällen handelt es sich ja bloss um einige Stunden, beim Fieber durch heisse Bäder um weniger als eine Stunde) mit so deutlichen Veränderungen reagiert. Besonders auffallend sind die Schwankungen der Erythrozytenwerte.

Es handelt sich sichtbarlich um eine vorübergehende Speicherung der Erythrozyten mit gleichzeitiger Ausschwemmung von Leukozyten. Deutlich ist, dass *parallel dem Absinken der Erythrozytenwerte die Lymphozytenwerte ansteigen*.

Zur näheren Ergründung der gefundenen Ergebnisse müssen noch zahlreiche umfangreiche Versuche ausgeführt werden.

Wahrscheinlich zeigt das Blutbild auch bei infektiösen Prozessen ähnliche Veränderungen. Da uns aber für die meisten Fieberkrankheiten das Blutbild vor der Erkrankung fehlt, hat man hierbei die einzelnen Phasen nicht so deutlich beobachten können.

#### **Zusammenfassung.**

Zur Erforschung der *Veränderungen des weissen Blutbildes und der Erythrozytenwerte beim Säugling und Kleinkind durch künstlich erzeugtes Fieber* wurde eine Reihe von Versuchen ausgeführt. Zur Erzeugung von Fieber wurden angewandt: heisse Bäder, Vollmilch-, Pyrifer- und Pyrisaninjektionen.

Beim Fieber durch heisse Bäder handelt es sich um eine Fieberperiode von ungefähr 1 Stunde. Wir sehen in fast allen Fällen mehr oder weniger deutliche Veränderungen der Blutformel: *ein deutliches Ansteigen der Leukozytenwerte, eine Vermehrung der Neutrophilen mit gleichzeitigem Absinken der Lymphozytenwerte*. Interessant ist die Tatsache, dass die Erythrozyten besonders empfindlich reagieren, auch in Fällen, bei denen das weisse Blutbild nicht sehr deutlich Veränderungen unterworfen ist. *Die Erythrozytenwerte können in kurzer Zeit stark*

zurückgehen (z. B. von 4 Mill. auf 3,2), um dann wieder ziemlich bald zu den alten Werten zurückzukehren. Besonders deutlich sehen wir das beim Fieber durch Vollmilchinjektionen auch in Fällen, bei denen das Ansteigen des Fiebers nicht stark ist.

Beim Fieber hervorgerufen durch Pyrifer- und Pyrisaninjektionen sehen wir ähnliche Veränderungen. Besonders auffallend ist im Differentialblutbild das starke Ansteigen der Neutrophilen. Hierbei haben die Kinder die Ausgangswerte der Temperatur und des Blutbildes im Laufe von 24 Stunden fast erreicht.

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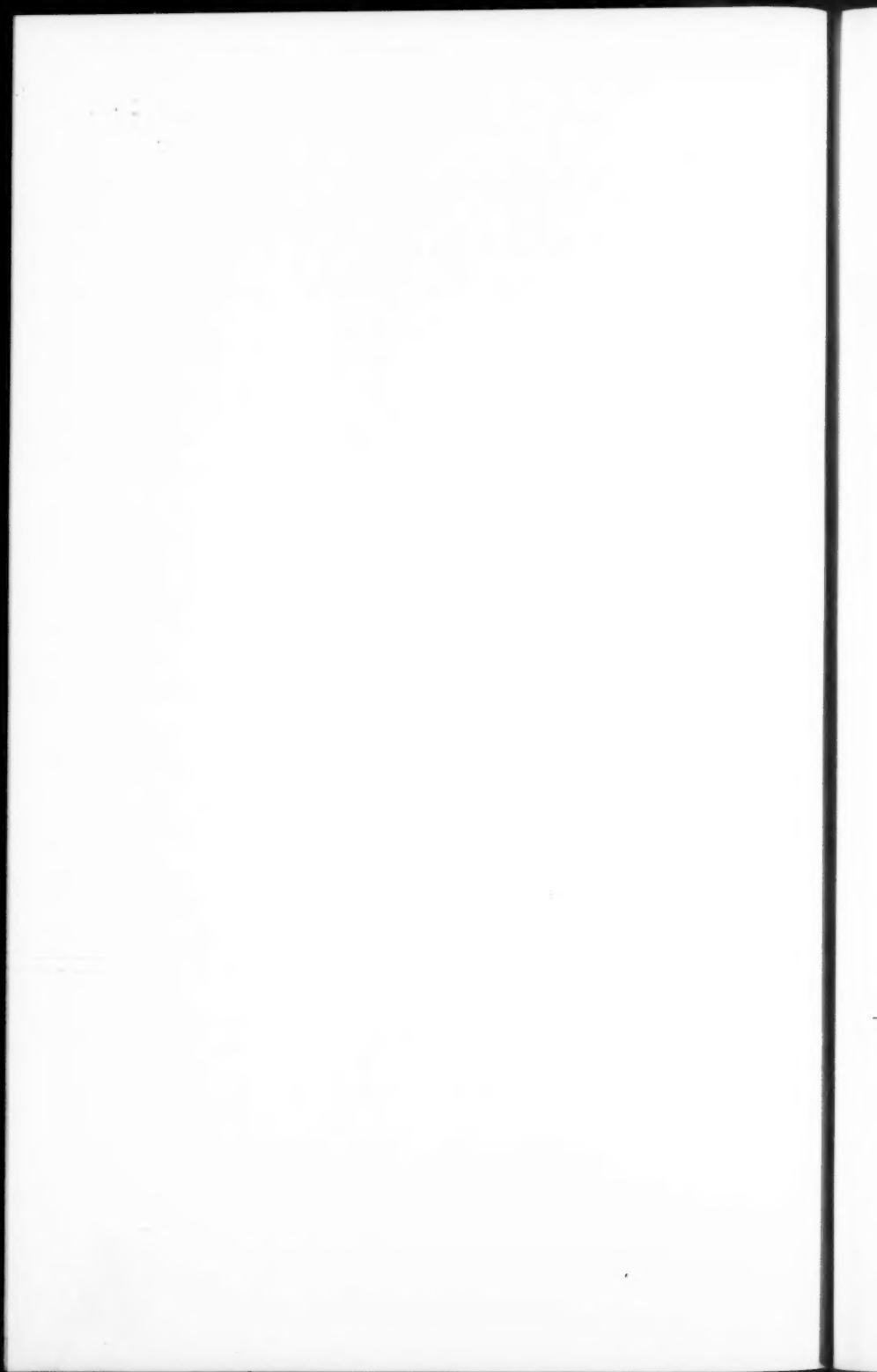
CLINICUM  
PAEDIATRICUM  
R. ACADEMIAE CAROLINAE  
MEDICO-CHIRURGICAE  
HOLMIENSIS  
1845—1945

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ACTA PEDIATRICA. VOL. XXXII, FASC. 5—4



OPERA  
PAEDIATRICA



# OPERA PAEDIATRICA

QUAS MEMORIAE DIEI QUO  
ABHINC CENTUM ANNOS HANC DOCTRINAM  
R. ACADEMIA CAROLINA MEDICO-CHIRURGICA  
HOLMIENSIS  
RITE TRADERE INSTITUIT  
DEDICAVERT PAEDIATRI SUECICI  
POSTRIDIE CALENDAS MAIAS  
MCMXLV

CURANTIBUS

*I. Jundell · A. Lichtenstein · A. Wallgren*

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ACTA PÆD. VOL. XXXII, FASC. 3—4

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UPPSALA 1945  
ALMQVIST & WIKSELLS BOKTRYCKERI AB

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## **An Outline of the History of Pediatrics in Sweden.**

By

**A. LICHTENSTEIN.**

Pediatrics is a belated shoot on the tree of medicine, the roots of which can be followed from olden times. True that we find in ancient documents a few directions and recommendations for the treatment of suckling women and their infants as well as regarding some diseases in older children, as in *Papyrus Ebers*, in the *Talmud* and in some Indian and Chinese authors. Also HIPPOCRATES (about 400 B.C.) deals with some children's diseases and their treatment. He considered that various diseases of infancy were due to difficulties in teething, a view which has persisted almost down to our own days.

Among most peoples, however, the general attitude was rather unfavourable to children, as for example among the ancient Greeks and Romans, who exposed unwelcome children, and among whom the fate of new-born girls — whether they should be allowed to live or not — was arbitrarily determined by the father. Even some of the ancient Swedish provincial laws concede such a right to the father. Among the Persians a certain rate of payment was fixed for the curing of men and domestic animals and a lower rate for women; but for the treatment of sick children no remuneration was given.

During the next few decades A.D., a number of authors, such as CELSUS, GALEN and especially the latter's contemporary SORANUS of Ephesus dealt with diseases of childhood. The last-mentioned author knew, for example, that natural feeding with the mother's milk will give a child greater resistance to disease, and

the advice he gives regarding infant hygiene in part holds good down to the present day. Also Arabs, such as RHAZES (about 900 A.D.), dealt with certain questions regarding the treatment of children. For example, he cautioned against weaning during the hot season.

Centuries elapsed before the knowledge of children's diseases began to be developed further than the stage reached by the ancients. From the fifteenth century three incunabula dealing with pediatric questions are preserved. Among them BARTHOLOMEUS METLINGER's »Eyn vast Nützlich Regiment der jungen Kinder« (printed at Augsburg in 1473) seems to be best known. But the first real handbook of pediatrics is »De morbis puerorum« (Venice 1518) by the Italian *Mercuriales*, a book of minor importance, which, however, was the sole detailed study on pediatrics for nearly 150 years.

During the seventeenth century some special works of pediatric interest were published, especially in England. GLISSON's famous treatise »De rachitide« (1650) and SYDENHAM's study on measles (1675) may be mentioned as examples. But it was not until the middle of the eighteenth century that pediatrics began to make any real advance. By that time the foundations of scientific medicine had been laid, with ALBRECHT VON HALLER's studies on physiology and MORGAGNI's on pathological anatomy. A seething development in different branches of medicine was proceeding and greater attention was being devoted to diseases of infancy and childhood. It was reserved for Sweden to make a contribution of the greatest interest in this field by the works of NILS ROSÉN VON ROSENSTEIN. In regard to him the Hungarian pediatricist VON BOKAY, in his »Geschichte der Kinderheilkunde«, writes that he was the first true representative of pediatrics and the real founder of that science.

At this time interest was being devoted to children's diseases also in other countries, especially in England, where CADOGAN, in his »Essay upon nursing and management of Children« (1750), and ARMSTRONG, in his »Essay on the diseases most fatal to Infants« (1767), preached the importance of hygiene and suckling; where WHYT in »Observations on the Dropsy of the Brain« (1768), for

the first time gives a good clinical description of tuberculous meningitis; and where the first clear description of poliomyelitis was given by UNDERWOOD (1784) in his »Diseases of Children», which was used as a textbook for decades.

But in the development of pediatrics none of those authors played such an important part as ROSÉN, by the publication of his work »Underrättelser om barnsjukdomar och deras botemedel» (Information about diseases of children and their cure). This famous book was issued in 1764 (certain parts of it had previously been printed in the almanack) and was not only published in a number of Swedish editions — the last as late as 1851 — but was also translated into Danish, German (6 editions), English, French, Hungarian and other languages, and was used in several countries as a textbook for more than half a century.

ROSÉN also deserves the credit for the introduction of real clinical instruction at the bedside, thus inaugurating a new era for clinical medicine in Sweden. Not till then could medical students receive their entire training within the country.

Though ROSÉN VON ROSENSTEIN may rightly be regarded as »the father of pediatrics», — and this not only in Sweden —, it was long before that subject had obtained an independent position and had won recognition on the same footing as other branches of study; indeed, in many quarters this is not yet the case. In the nineteenth century the French, with GUERSON PÈRE, BILLARD, TROUSSEAU, BARTHEZ, RILLIET and others, took the lead in pediatric researches, which perhaps was largely due to their clever utilization of the abundant material for study in the Paris hospitals for children and foundlings. Numerous studies and textbooks on children's diseases were published also in Austria, Germany, Holland, England, Switzerland and Sweden. But pediatry still completely lacked academical representatives, and the students received no instruction in the diagnosis and treatment of children's diseases, apart from lectures by some maternity doctors on diseases in new-born children. It had in fact been prescribed in the Royal instructions of the 19th August 1761 for the »Director of Midwifery» in Stockholm, that he should »in every term give lectures to medical students on the diseases of lying-in



women and of infants». In those days, however, no systematic instruction on the diseases of children was imparted.

At a somewhat earlier date the Swedish authorities had had their attention directed to the high infant mortality in Sweden — at that time it was over 20 per cent. that is, nearly ten times as high as now. In 1778 an abortive attempt was made in Stockholm to arrange a kind of polyclinical instruction on the diseases of children.

But not till after the lapse of another whole century was any real instruction on the diseases of children organized here, and yet Sweden in this respect was in advance of any other country. Certain tentative attempts, however, can be traced to a somewhat earlier date. Thus in the Statutes of Karolinska Institutet of the 11th December 1822, it is prescribed that the students before the »Master of Surgery» examination should for two months visit »Allmänna Barnhuset» (then a foundling asylum) at times when the doctor was making his rounds there and when vaccination was being performed. However, it was only instruction in vaccination that was imparted there — not in the diagnosis and treatment of children's diseases.

After a few abortive attempts in the eighteen-thirties to create a pediatric clinic, Karolinska Institutet took up the question again in 1842. In a memorial, which was strikingly in advance of the times, the professors laid stress on the very considerable differences between the diseases of infants and older persons and emphasized the necessity of a clinic for children where instruction in pediatrics could be imparted at the bedside.

The words in which this memorial was couched heralded the dawning of a new day. It is perhaps no coincidence that the country of ROSÉN VON ROSENSTEIN led the way in recognizing pediatrics as an independent branch of study and in organizing obligatory instruction in the subject for medical students. But much enthusiasm and personal power was required to carry through a reform, although the necessity of it had been recognized by Swedish authorities and doctors, in advance of other countries. The man who by the strength of his personality succeeded in overcoming the obstacles raised on many sides, and who

has won imperishable fame as a pioneer in the development of pediatrics into a separate branch of study, was FREDRIK THEODOR BERG.

The 2nd May 1845 is a red-letter-day in the history of pediatrics. The pediatric clinic of Karolinska Institutet was then opened at »Allmänna Barnhuset» in Stockholm, and Berg, who since 1842 had been the head doctor at that institution, in the capacity of the first professor of pediatrics started there a course of instruction, which from the outset, as also the examination on the subject, was obligatory for all medical students. Pediatrics had been recognized as an independent subject, on the same footing as other branches of medicine, and Karolinska Institutet has the honour of being the first medical school in the world where that happened.

The foresight thus shown in Sweden is so much the more admirable as in most other countries many decades elapsed before pediatrics were recognized as an obligatory subject of instruction and examination; indeed, in many quarters this has not yet been done. Thus, for example, in 1909 only 11 out of 20 German universities had a professorship in pediatrics, and no special examination in that subject was required. Nor was this as yet the case in France. In England there are still merely 5 professorships of pediatrics and in the 1944 Report of the Inter-departmental Committee on Medical Schools a complaint is made that »generally in the medical schools in Great Britain the teaching about children has been inadequate and only a faint interest has been taken in the subject. The inadequacy has been due in part to lack of facilities for the study of the subject», and it is emphasized that »if the place of pediatrics in the undergraduate course is to be assured, adequate recognition must be given to the subject in the final qualifying examination».

In 1849 Berg retired from his post as head doctor, having been appointed to be a member of the Medical Board, but he continued his duties as professor till 1854. Among his merits in regard to the promotion of pediatric instruction, we note that in 1851 he took the initiative in the establishment of a pediatric polyclinic, which proved to be of the greatest importance in that respect.

Berg was succeeded by HJALMAR ABELIN, who died in 1882. Some twenty years previously an assistant mastership in pediatrics had been created. The man designated as the first holder of this post was ADOLF KJELLBERG. He began to give instruction in this subject as from 1864. In 1879 the assistant mastership was converted into a temporary professorship and in 1909 into a permanent post. Thus from that date Karolinska Institutet has two professorships of pediatrics, and this at a time when a large number of universities in many countries were entirely without a permanent representative of that subject. Certain attempts made to suppress one of these professorships were fortunately frustrated. From the year 1882 clinical pediatric instruction was imparted at Kronprinsessan Lovisas Children's Hospital, which since that time has served as one of the pediatric clinics of Karolinska Institutet. The successive holders of these professorships at that Institute were Oscar Medin 1884—1914 (during the first year temporary professor), Jonas Wærn 1885—1914 (1885—1908 temporary professor), I Jundell 1914—1932, Wilhelm Wernstedt 1921—1927, A. Lichtenstein from 1932 and Arvid Wallgren from 1942.

The term of service at the pediatric clinic was fixed in 1845 at four months, with two hours' clinical instruction and two lectures a week. When the pediatric polyclinic had been established, some of the instruction, under ABELIN's supervision, was transferred to it. In 1907 the teaching course was eked out with two weeks' service as clinical assistant; this regulation, however, was afterwards unfortunately abolished. Now the term of service at the pediatric clinic is reduced to three months; on the other hand, it is required that the professor shall give four two-hours lectures a week.

At Upsala a temporary professorship of pediatrics and practical medicine was instituted in 1877. No pediatric clinic was established, but as from 1884 merely a polyclinic, where instruction in pediatrics was imparted. In 1915 a provisional children's department was opened, and in 1924 an independent pediatric clinic. Not till 1943 was an independent professorship of pediatrics instituted. The successive holders of that post were

O. V. Petersson 1884—1909, Gunnar Forssner 1911—1912, Ragnar Friberger 1913—1915, Gustaf Bergmark 1916—1921, and Ivar Thorling 1933—1943; its present holder is Curt Gyllenswärd.

Somewhat similar developments took place at Lund. In 1879 a temporary professorship of pediatrics was created. The instruction given was merely of a polyclinic character. A clinic was established in 1899, when a children's hospital was erected by private initiative; it was used for clinical instruction as from 1900. At the present time an entirely new clinic is planned. The temporary professorship of pediatrics, which also included instruction in practical medicine, was made permanent in 1916. In 1937 it was converted into an independent professorship of pediatrics. The successive holders of this post were Seved Ribbing until 1888, C. H. Hildebrand 1900—1916, Kjell Otto af Klercker till 1937, and afterwards Sture Siwe.

Instruction regarding infectious diseases of children is, of course, one of the most important branches of pediatrics. As such diseases comparatively seldom occur in children's clinics and polyclinics, the training of the medical students was formerly somewhat defective. This shortcoming, however, was remedied by the introduction, as from 1911, — at the proposal of Karolinska Institutet, — of one month's obligatory service at the hospitals for infectious diseases at Stockholm, Gothenburg, Upsala or Lund, where instruction is imparted by the head doctor.

At the time when the pediatric clinic was instituted, there was no children's hospital in Sweden. In this country, as in other countries, the public care of children had long been restricted to homes for children and foundlings. It was therefore natural that the first clinic for children was established at »Allmänna barnhuset», which had developed from the »Barna- och Tucktohus», established by Gustavus Adolphus in 1624, and which was at first a reformatory for physically and morally defective older children, whose medical treatment was confided to a barber-surgeon. In course of time, however, it was converted into an institution for the care of healthy infants, who, as they grew older, were boarded out under continued supervision.

In the eighteenth century increasing attention was devoted to

the medical treatment of children, and in 1752 the City Medical Officer of Health in Stockholm was instructed by a Royal Letter to visit »Allmänna Barnhuset» at least two or three times a month.

At the time when Berg in 1842 began his work as head doctor of that institution, the conditions there were deplorable, but were speedily and radically improved by Berg. The change is described by MEDIN in the following words: »When we study old records from 'Allmänna Barnhuset', we cannot fail to fall into astonishment and admiration at the sweeping change which took place when Berg commenced his duties there. Before the year 1852 we find in a kind of register some meagre records indicating the causes of death, such as dental convulsions, tabes and the like, as the sole memorial of the medical science of those days. What a splendid advance was made in the year 1842! And how admirable is it that Berg, without the slightest support from any preceding tradition, could all at one create an entirely modern clinic. He immediately introduced separate records for each infant on a kind of printed form which is in use to this very day. Berg evidently had a very keen power of observation, his descriptions are always objective and the diagnoses thoroughly scientific. As from the year 1842 postmortem reports on the infants who had died at the hospital have been drawn up. Berg performed the postmortems himself, wrote the reports with his own hand and recorded in minute detail the pathological-anatomical diagnoses, all with great accuracy and scientific skill. In this respect he was an example for the clinicians of his time and, indeed, of all times.»

In 1885 »Allmänna Barnhuset» moved into a new building in Norrtullsgatan, thus obtaining far greater resources for medical treatment and instruction.

However, »Allmänna Barnhuset» was not as yet a real hospital for children. It was intended chiefly for healthy infants, as well as for the older children who had been boarded out and required medical attendance. As from the year 1919, however, sick children from outside were to some extent admitted. But not till its reorganization in 1931, when it was taken over, under the name of Norrtulls Sjukhus, by the City of Stockholm, did it become a real hospital. Here one of the pediatric clinics of Karolinska

Institutet is continuing its work, pending the establishment — as we hope, within a few years —, of the new clinic for the erection of which provision has been made in a bill passed by the Riksdag in 1944.

In other countries the first real hospitals for children had been established in the early part of the nineteenth century. The very first was »Hôpital des Enfants Malades» in Paris, which was instituted in 1802 by Napoleon and was followed in 1834 by the Nicolai Children's Hospital in the then St. Petersburg, in 1837 by St. Annenspital in Vienna and in 1839 by the children's hospital in Budapest. In the eighteen-forties and fifties a small number of children's hospitals were established in Germany, England and France.

In Sweden the first real hospital for children, namely Kronprinsessan Lovisas Children's Hospital, was established in 1854. It was built, equipped and for a long time maintained entirely with the aid of private donations. This hospital had at first 30 beds and an infection ward with 10 beds. Its first head doctor was MAGNUS HUSS, Professor of Medicine at Karolinska Institutet. It is interesting to note that in accordance with the regulations, only children between the ages of two and eight were admitted, and that at that time it was considered unwise to bring a number of sick infants together in a general ward, in view of the inevitable risk of infection.

As early as 1859 Gothenburg too had a private children's hospital with 12 beds.

The first children's hospitals in the country had thus been erected entirely by private initiative and with the aid of private donations. The costs of maintenance were also defrayed in this way for many decades ahead, and several children's hospitals erected later were entirely supported by private charity.

Despite the astonishing lack of interest on the part of the public authorities, private hospitals for children rapidly developed, thanks to a copious influx of handsome donations. Kronprinsessan Lovisa's Children's Hospital and the Gothenburg hospital for children were extended and enlarged. The former was extended in 1897, so as to comprise a medical and a surgical department, with

altogether 150 beds. The hospital at Gothenburg, after similar extension, provided accommodation for 240 children. These two hospitals have done very extensive and highly important work in the service of the medical care of children. In course of time some new private hospitals for children were erected.

The generous contributions made by private donors in this country towards the establishment and maintenance of children's hospitals deserve to be put on record here with the deepest gratitude.

It should be observed, however, that only in a few of the larger towns, notably Stockholm, Gothenburg, Malmö and Helsingborg, did resources suffice for this purpose. The rest of the country was completely destitute of such hospitals. As the public authorities had failed to realize their obligations towards sick children, hospital care in this country had developed into a magnificent organization for the medical treatment of adults, staffed with specialists in different branches of medicine, but without any resources whatever for expert medical treatment of children's diseases.

In this regard, reform was long delayed. The efforts made by isolated individuals to arouse the interest of the public authorities in the provision of organized hospital treatment for children failed to meet with any response for years. Thus, for example, at the annual Meeting of the Swedish medical Association at Stockholm in 1922, when hospital organization was under discussion, I stressed the crying need of special wards for children and, as an urgent desideratum, summed up my wishes in the words: »A children's ward at one hospital in every county.» But the time for the realization of that project had not yet arrived.

In the course of the last twenty or thirty years the resources of private charity, owing to sweeping changes in social and economic conditions, have been greatly reduced, whilst, for a variety of reasons, maintenance costs have alarmingly increased. It gradually became evident that satisfactory hospital treatment could no longer be provided on a charity basis, but would require large contributions from the State and municipal authorities. The existing private hospitals for children were compelled, in in-



creasing measure, to apply for municipal support. And in the larger towns, such as Stockholm, Gothenburg and Malmö, the requested subsidies were granted on a generous scale.

Demands that hospital treatment for children should be extended to the entire country became more clamorous and now began to meet with ready response. The Government Committee on Hospital Treatment, in their Report of 1934, approved the plan of establishing at least a ward for children, under the superintendence of a qualified pediatrician, at one hospital in every county. The Medical Board then drew up a proposal on very similar lines, suggesting that the children's wards should be established and maintained with the aid of State contributions. These contributions were to be payable at a rate based on the provision of two hospital beds for children per 10 000 inhabitants. This proposal, having been sanctioned by the Government, was passed by the Riksdag in 1939.

So now we pediatricists are rejoicing to see one children's ward after the other being established in rapid succession in different parts of the country. — At present the number of children's hospitals and children's wards in Sweden is 24, with altogether about 1 300 beds. Plans for several new such wards are now in an advanced stage, and we can discern near at hand the time when no county in Sweden will be without a hospital containing a special ward for the medical treatment of children.

Not till then will facilities have been created for the distribution of competent children's doctors all over Sweden. The number of qualified children's doctors in this country, with its population of 6 597 000 souls, is barely more than a hundred, and they are very unequally distributed. No less than 40—50 of them reside in Stockholm, altogether about 30 in a few of the larger towns, whilst 20—30 are spread over the remainder of the country. Some counties are still completely devoid of children's doctors. Whereas the larger towns have one pediatrician per 15 000—25 000 inhabitants, large groups of the population, comprising hundreds of thousands of souls, still completely lack facilities for convenient access to the prompt assistance of children's doctors in emergency cases. Among the counties most



poorly provided in this regard are those in the north part of Sweden, where the birth rate, as well as the mortality, is considerably higher than in other parts of the country.

In my opinion, the number of children's doctors in Sweden is still quite insufficient. The real need, I am convinced, is at least treble the actual number, and I do not think we shall be much mistaken in predicting that the day will come when several hundred well-trained children's doctors in all parts of the country will be devoting their energies to the prevention and cure of children's diseases. These doctors will work not only in children's hospitals, but also in various institutions where children are cared for, such as children's homes, child welfare centres and schools. Also the mental care of children will largely require the cooperation of children's doctors.

The greatest obstacle at present to a large increase in the number of pediatricians is that at our children's hospitals the facilities for training are inadequate. State and municipal aid will be needed with a view to the speedy establishment of a larger number of posts at children's hospitals and wards, in order to meet the demand for training in pediatrics. This is all the more necessary as, after the final university examination, provision must be made not only for intending specialists on the diseases of children, but also for large groups of candidates for appointments in the medical public service, who in the course of their duties will be greatly in need of pediatric and social training. In this thinly populated country it can — for economic reasons —, scarcely be expected that pediatric and social work could be carried on solely by specialists. It is therefore highly desirable that candidates for medical appointments in the public service should receive the best possible training in pediatrics.

A comparatively new field for children's doctors is the care of new-born children in maternity hospitals and wards. This field had long been a »no man's land«, intermediate between that of the obstetrician and the pediatricist. Though individual obstetricians have shown interest in the problems of the first-weeks period, these problems have long remained but little investigated. And yet, in this field there is still much to be done. We need merely

consider that the mortality during the first two weeks after birth, in sharp contrast to the mortality during the entire first year of life, has not fallen at all, or at any rate quite slightly.

In the course of the last twenty or thirty years, however, children's doctors have been appointed as consultants in some lying-in departments. A Swedish pioneer in this field is Professor HJALMAR FORSSNER, who in 1917 established a pediatric consultative post at the general maternity hospital in Stockholm. It is only within the last few years that similar posts have been established at other lying-in departments in the country, and that consideration is being paid to the need of specially equipped premises for the care of children. It is my hope that it will not be long before pediatric science throughout country will be turned to account also for the care and treatment of new-born children.

Swedish pediatricians have made important contributions to scientific research in their field of work. I shall confine myself here to mentioning a few examples, namely BERG's discovery of the thrush fungus (the cause of thrush in children), ABELIN's and KJELLBERG's numerous reports on the diagnosis and treatments of children's diseases, MEDIN's classical investigations into infantile paralysis, which have associated his name with that disease, VON HOFSTEN's great work on cholera infantum, ULRICH QUENSEL's thorough pathological anatomical studies on infants, IVAR WICKMAN's famous studies on the epidemiology of infantile paralysis, THURE HELLSTRÖM's excellent works on diphtheria, JUNDELL's and his disciples' thorough investigations into the metabolism of infants, WERNSTEDT's extensive investigations into the pylorospasm and ERNBERG's fundamental studies into the connection between erythema nodosum and tuberculosis.

Ever since the time of ABELIN and MEDIN, Swedish pediatricists have participated with interest in the popularization of the advances made in pediatrics, thereby greatly contributing to spreading knowledge regarding care of children in wide circles in this country.

In the course of the last few years scientific work in pediatrics has flourished in our country. This is indicated by the long row of volumes of *Acta Pædiatrica*, which under the editorship of

JUNDELL, for 25 years has transmitted the results of Swedish pediatric research to the greatest part of the civilized countries. The jubilee volume of *Acta Pædiatrica* contains 49 studies in various branches of pediatrics by 50 authors from 19 children's hospitals and institutions, a testimony that scientific work is now being carried on with success not only in university clinics, but also in children's hospitals all round the country. This is a guarantee that practical pediatric work in Sweden is being maintained at a high level and well turns to account any progress made in this field.

In conclusion, a few desiderata. The medical treatment of children must be better provided for by the establishment of a larger number of children's hospitals and children's wards in this country. In this way provision will also be made for the urgent need of a larger number of posts affording facilities for pediatric training.

As regards education, we hope first and foremost for a larger number of teachers. Assistant teachers should relieve the professors from too much propædæutic instruction, so that they have more time left for scientific work. As a further desideratum, I propose the reintroduction of the servise as clinical assistant in pediatrics, as well as extended and improved instruction regarding epidemic diseases, child psychology and psycho-pathology as well as social pediatrics.

Our aim should be that every Swedish child at need shall receive the benefit of the expert knowledge of a well-trained children's doctor and shall, if necessary, be treated at a children's hospital under the supervision of a qualified doctor. The Swedish authorities have shown in the past that they consider it to be the interest of the country to take good care of her children, those who are to be the workers of tomorrow in the fields of mental and material culture. The capital invested in improving the care and medical treatment of children will certainly be well-spent money.

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## **Social Welfare of Swedish Children, Past and Present.**

By

**A. WALLGREN.**

Our knowledge of the way children were taken care of and reared in Sweden in ancient times is completely in the dark. Only a few particulars of the kind of life our ancestors lived, have been transmitted to us, and these are the only sources from which we can draw some information as to the care of children at that epoch. The home was run on a principle of family dictatorship. The father ruled over the child, and if for some reason he considered it undesirable, he could rid himself of it by exposing it. Merciful people might in pity rescue it and take charge of it. In remote antiquity, neither Sweden nor any other country in Europe thought of interfering with the way children were reared and cared for. A child's life was not highly evaluated at that time, and children had no rights.

About the year 1000, after the introduction of Christianity, moral improved and the people's outlook on life became more humane. A reaction against brutality and cruelty, and even against the custom of exposing children made itself felt. Not until a hundred years later, however, was this custom forbidden by law. The intensified humane spirit found expression in providing for the poor and defenseless. Merciful people included even children in their relief work. Some were placed as foster-children in private families, others again were confided to homes for the poor, or admitted to hospitals which, as a rule, were affiliated to convents and destined for the care of adults. In reality, a child probably did not profit much by these latter measures. Viewed in the light of our present knowledge of the

great risks a child runs when nursed in a ward together with adults suffering from all kinds of diseases, the assumption is justifiable that this way of providing for children took a heavy toll amongst them.

Not until the 17th century were communities bound by State regulations to assist children in distress and to provide for the establishment of institutions designed solely for the housing and care of infants and children. From information gathered from some historical documents it may, however, be assumed that there existed before that time a few convent-hospitals solely or principally for the care of children.

In 1624, a decree was issued forbidding the admittance of healthy children to hospitals for adults. Under this law, children were to be cared for in special homes. Five years earlier, it had even been decreed that such homes were to be established in towns, and later on regulations were issued providing for such institutions even in the country. Owing to the economical crisis in Sweden at that time — a sequel of the Thirty years' war — these measures could not be put in force. Only one orphanage, in Stockholm, was established, and this was, of course, utterly inadequate to serve the needs of the large number of children in need of help at that time. Besides, five years later it was closed, because of lack of funds. The extent of the lack of understanding of the needs of children existing at that epoch, is significantly illustrated by the fact that this home for children was also supposed to offer shelter to loafers, whores and other criminal individuals. The majority of the children who were not adequately cared for by their families, were placed in homes for the adult poor which, at that time, were rather numerous and scattered all over the country. Such arrangements were at that epoch considered to be the normal and correct manner of providing for a defenceless child.

Nor did the establishment of a new State orphanage in Stockholm in 1638 effect a lasting change for the better. Only a few years after its foundation, criminals were again admitted and housed together with distressed children. The institution was called »Kronobarnhuset» and was originally designed to receive

children from the entire kingdom. In reality, it only housed the destitute children of Stockholm. Only two more institutions designed for the care of children were established in the course of that century, and these were situated in country towns. These institutions were not only run irrationally and incurred, therefore, heavy expenses, but the nursing and fostering of the children were also most unsatisfactory. About the middle of the 18th century, however, another ten homes for children were established in different parts of Sweden. Of these, the one in Malmö accommodating a hundred children, and the one in Stockholm, the so-called »Politibarnhuset», were the largest. The latter was chiefly intended for the care and nursing of infants. A few decades later the »Kronobarnhuset» and the »Politibarnhuset» were fused into one institution called »Allmänna Barnhuset». Apart from confiding to the above mentioned institutions children who could not be left in home- and private care, it was still usual in the 18th century to place these children in public homes for the adult poor.

Considering the unsatisfactory results obtained by confiding the care and rearing of children to the orphanages, and in view of the heavy expenses the management of these entailed, it was quite natural to look for a more profitable investment of the means at disposal for children's relief work. Death took a heavy toll amongst the children living in the homes for children. It was estimated that every other child admitted to any one of these institutions died there. This situation gave rise to a preference of boarding as many of these children as possible out with private foster-parents.

With a view of preventing as far as possible, a premature death of infantile boarders at the nurseries, the services of wet-nurses were engaged in 1788, and 12 years later it was stipulated in the licence to run the »Allmänna Barnhuset» in Stockholm that infants resident there, should be nursed and brought up by wet-nurses. Wet-nurses were at disposal at the ratio of approximately 1 to 1½ children. In the beginning, the wet-nurse was not allowed to have her own child with her. After having been weened as new-born, it was billeted in a

foster-family. In general, such an infant was doomed. Not until the beginning of the 19th century was the wet-nurse entitled by law to have her own child with her and to enrol it as a boarder in the institution.

As a rule, medical health supervision was not provided for in such institutions, and as regards the »Allmänna Barnhuset» in Stockholm, a physician in the capacity of medical adviser was appointed as late as 1758. Owing to the unsatisfactory manner in which the »Allmänna Barnhuset» in Stockholm was run, the motion was brought forward to reorganize it. Several of the remaining childrens homes were closed. The placing of distressed children as boarders in private families was more and more adopted as the normal procedure. Thus the »Allmänna Barnhuset» became in course of time a centre where children were collected and put under medical control before being boarded with foster-parents. Under the Act passed in 1766, the »Allmänna Barnhuset» was supposed to keep in its care only infants and such children as could not be placed as boarders in families. This is in complete agreement with the scope of similar institutions of present times.

In the cours of the 18th century measures were taken by the public to improve the welfare of children who were not admitted to orphanages. These measures marked the beginning of public activity within the sphere of relief work for the benefit of children. In the year 1749, the Tables of statistics of the population in Sweden expressed in figures the naked fact that the mortality rate in infants was appalling throughout the whole kingdom. On the average, every fifth child died in its first year. This situation produced an intensification of the interest in the care of children and enhanced the desire to ameliorate their conditions of life. It was also made evident that it was not only the children admitted to public nurseries who had poor prospects of survival.

In the course of the 18th century, the financial situation of Sweden gradually took a turn for the better. Trade and commerce began to prosper. This helped towards a more satisfactory provision for the children's welfare. Increasing enlightenment and human progress was followed by an improved understanding of



children's needs and requirements. Two physicians of world-wide repute, professor Carl von Linné and professor Nils Rosén von Rosenstein, both of Uppsala, are responsible for the revival of the art of medicine in Sweden. The works of the latter in particular had a significant influence on the improvement of the care of children. In conformity with the trend of the epoch, it was thought that by helping towards the enlightenment of the people, an amelioration of conditions would follow, and a valuable aid in imparting vital knowledge to the masses constituted at that time the small popular calenders in Sweden called »Almanachs». During the years 1733 to 1771, Rosén von Rosenstein published in these »Almanachs» continuous »information concerning children's diseases and their treatment». These publications are to be considered as the first mass-pamphlets dealing with the essentials of the care of children. Later on Rosenstein collected these articles, and in 1764 he published them in book-form. This book was translated into several languages and it became one of the most popular manuals of pediatrics in Europe of that time.

In the 18th century, it was not unusual for both parents and authorities to be lacking in solicitude for the welfare of children and who were, consequently, badly neglected. A new law was therefore promulgated by which it was hoped to further the protection of children. Under this a penalty was imposed on any mother who neglected to feed her child on breast-milk for at least 6 months if the child contracted a lethal disease owing to the discontinuance of breast-milk feeding. At that time home- and private care of children was assisted by grants in aid as well to children who were cared for by their parents and as to those who were boarded with foster-parents. These allowances were paid through the intermediary of »Allmänna Barnhuset», through the intermediary of private persons or private institutions and communities. The obligations of the communities, however, were very limited. Not until 1760, when the Poor-Law was issued, was every community constrained to provide for the poor and destitute including distressed children resident within its own district.

The illegitimate child was in the most precarious situa-



tion of all. Mortality among illegitimate children was approximately twice as high as amongst legitimate children, and infanticide was not infrequently practised. With a view to remedying these deplorable conditions, regulations for the protection of illegitimate children were issued in the year 1778. Under these among other things, clergymen and mid-wives were bound not to divulge the identity of the mother.

The still high death-rate figures, however, were sufficient evidence that the results obtained were by no means as encouraging as had been anticipated. This was, no doubt, due partly to the ignorance of the people, and partly to their indolence, as well as to the prevailing low standard of living. Since even the knowledge of physicians and public instructors was still rather incomplete at that time, its application such as it was to the sphere of children's health and welfare could hardly be expected to have a remarkable effect on death-rate.

The 19th century was signalized by rapid intellectual progress and increase of material prosperity. Industrialism received a new stir by which public wealth accumulated. These circumstances resulted in a reorganization of social life, and, in consequence, the individual standard of living was raised. Class distinction began to disappear. In 1842, public elementary instruction was made compulsory. The foundation of public high schools for the people, the creation of professional schools, the widening of the university and high school curricula and the foundation of the medical school in Stockholm »Karolinska Institutet» in 1815, offered a propitious ground for intellectual pursuits. The provision of facilities for learning and the increase of material prosperity were also reflected in the care and rearing of children. One of the active factors in this development may have been the progress in the science of medicine in the latter part of the 19th century. The fresh impulses which this science had received had a bearing on the death-rate which fell generally throughout the whole country.

In the orphanages, however, the death-rate still remained appalling. In the middle of the 19th century, every third infant of the infants boarded in the »Allmänna Barnhuset» in Stockholm died, in spite of the general adoption of breast-feeding. The

death-rate in the orphanages in country-towns, most likely was still higher, since they did not benefit by the solicitude of resident physician of »Allmänna Barnhuset» F. T. Berg, one of the most energetic and broad-minded physician of his day. His services had been engaged in 1839, and right from the beginning of his activity at the »Allmänna Barnhuset» he showed strong opposition towards the way in which this institution was conducted and towards the objectionable conditions existing there. Gradually, his criticism and reformatory measures attracted attention. New doubts arose as to whether the collective-care of children in institutions really gave adequate protection for the child's health and welfare. The childrens homes in the country gradually discontinued their activity. Towards the end of the 19th century, apart from the »Allmänna Barnhuset» in Stockholm, there remained only two of the old ones which still were in activity.

The progress made in the knowledge of the proper care of infants and older children, and the practical application of the experience acquired in this sphere, even had a favourable influence on the chances of survival of the children in collective care in institutions. During the latter half of the 19th century, people gradually began to be less afraid of confiding their children to the care of the new founded institutions, called infants or childrens homes. Interest was kindled again to found such institutions for children. With the aid of private means, which as a rule, were raised through the intermediary of philanthropic societies, a number of new homes for children were founded, in particular in cities. At the turn of the 19th century, there existed, about 160 homes for children in Sweden. A large number of children, however, who were in charge of country-communities, were boarded in their own district homes for the poor.

In the course of the 19th century, the first institutions providing for non-resident (s. c. »half-open care») infants and children were established. In the year 1836, on the initiative of private persons, nursery-schools for pre-school children were established in Stockholm. Gothenburg soon followed the example of Stockholm, and so even did several country-towns. To England must be given the credit of being first in the founding of

such nursery-schools. To these, children between the ages of 4 and 6 years were admitted, and the activity of these schools was directed towards a pedagogical, as well as a social point of view. In 1854, on the initiative of Magnus Huss, professor of medicine, the first day-nursery was established with private means, in Stockholm. Subsequently, day-nurseries were established in rapid succession in towns and industrial districts. The funds for the majority of these were raised by private institutions which were frequently supported by the communities. The day-nurseries were designed to receive children whose mothers had an professional occupation, but nobody to look after them during their mothers' absence from home. In 1896, the first »Kindergarten» on the lines of the German model was established in Stockholm. This was intended for children of well-to-do families and its scope included care and pedagogical education of the children.

In spite of the progress in every province which characterized the 19th century, more particularly the latter part of it, the care of children at that time and at the turn of the century was marked by great deficiencies. These were due to the fact that it was still not fully understood that childhood was a particularly characteristic period of life. Not until the beginning of the present century was this gradually realized. Professor Jundell stated that the progress in the sphere of pediatrics proper during the first decade of the 20th century surpassed that gradually achieved during the preceding milleniums. This advance was further marked by a deep interest in the development of the child's soul, and greater attention was paid to the child's mental disorders.

At the initial stage of the reorganization of children's care and fostering attention was focussed especially on the still appalling high death-rate among infants, in particular among those boarded with foster-parents, and on the increasing dissoluteness of juveniles. At that time, new regulations were claimed, and in 1902, Parliament passed two very important Acts, namely, one Infant Care and Fostering Act and one regulating the Education of Debased and Depraved Children. Fifteen years later, the Act regulating the Adoption of Children and the Rights

of Illegitimate Children was passed. Under the latter Act illegitimate children were entitled to education and professional training corresponding to the socio-economic status of their parents. In 1924, a bill was passed, the Children's Welfare Law, imposing on communities the duty of undertaking welfare work amongst children. This bill is still in force. In 1934, an additional law was passed by which communities were forced to extend such welfare work to certain juveniles between the ages of 18 and 21 years. This year (1945) Parliament will have to deal with a motion claiming further completion and modernisation of the Children's Welfare Laws, in particular those regulating the care of foster-children and collective care in institutions. These laws contain clauses stipulating in detail the duties and responsibilities of the communities in regard to distressed and depraved children and juveniles, and the manner in which these are to be executed.

Institutional-, private home-care and fostering has in many respects been improved in the course of the present century. A campaign was started to enlighten the public on the essentials in the rearing of infants and older children through the medium of brochures, classes, broad-casting lectures and cinemas. One detail of great importance in this campaign was the education of mothers in so-called »demonstration-classes» of the proper care and fostering of their infants and children. This method of enlightenment has been practiced for several decades in all parts of Sweden. These ambulatory classes which extend over a week, are held by qualified teachers in child care and fostering, and are attended by interested mothers who thus received fresh impulses from this specialized tuition. For some years past these classes has been arranged principally for prospective mothers belonging to the maternity welfare centres.

In 1901, a new type of »open» institution of infant welfare was established in Stockholm the so-called »Goutte-de-Lait». This was supposed to act as an advisory and consultative source for mothers. Others were established in rapid succession in several large towns of Sweden. At one time, there were as many as 40 Goutte-de-Lait institutions existing in Sweden. These were scattered about 27 different places. One of the principal

tasks of these institutions was to provide infants with adequate artificial diet. Until the World War No. 1, the Goutte-de-Lait institutions were rather popular and had a wide field of activity. Gradually, however, the demands on them decreased, and some of these institutions were closed. Their task was fulfilled, since mothers were by then sufficiently experienced and could easily be taught the formula for an adequate baby diet and easily prepare the diet in her own kitchen.

Some of the Goutte-de-Lait institutions at that time reorganized their activity by directing it more to the enlightenment of the nursing mother and to the discouragement of premature weaning. Gradually, all these Goutte-de-Lait institutions were reorganized in this manner and turned into the so-called infant welfare centres. The two institutions differed inasmuch as the scope of the Goutte-de-Lait institution did not include any arrangements for home-visiting. The children's welfare centre, however, disposed of a visiting nurse and a physician. The former controlled the rearing of the child in the child's home and advised the mother, whereas the physician controlled the condition of the child and the directions of the nurse in the surgery affiliated to the institution. In the succeeding years several new infant welfare centres were founded, more especially in the more important towns of Sweden.

In the year 1923, the Section of Pediatrics of the Swedish Society of Physicians submitted to His Majesty the King a petition requesting the establishment of further infant welfare centres. With a view to reorganize all infant welfare centres existing at that time in Sweden, the Board of Health in 1935, submitted a motion for a State allowance. Two years later Parliament passed this Act.

In the 7 years which have passed since then, this special service for the protection of children's health has been established in almost all parts of Sweden, in the provinces as well as in the more important towns. They were supported by a State allowance enabling them to expand their activity and to provide for the distribution of prophylactic medicines and vitamins such as, for instance, vitamin D. Any child was admitted, irrespective of

its socio-economic level. The infant welfare centres became very popular and in the places where they operated, approximately 90 to 100 per cent of the resident children were followed up. In the beginning only infants were admitted. Later on even children aged from one to three years — in some districts up to seven years — were controlled. In almost all districts it is compulsory that foster-children belong to the children welfare centre of the district by means of which a very satisfactory supervision of these children is attained. In 1943 all in all 93 054 infants out of 120 000 new-born babies were brought to the services of the 944 infant welfare centres existing at that time. As a result of the propaganda concerning the value of breast-feeding carried on by these centres 74 per cent of the infants are now fed on breast-milk alone during their first 2 months of life and 43 per cent during the first 6 months, and a very large percentage of the remaining infants receive complimentary feeding. The State allowance for this welfare amounts to 1.5 millions Sw. crowns this year.

The welfare of children over 7 years of age is nowadays controlled by school-physicians. As early as the 19th century the schools in the more important towns of Sweden engaged the services of physicians who in the capacity of visiting physicians had to supervise the health of school-children and the sanitary conditions of the school. Owing to deficiencies in the organization and the modesty of the fee, the physician could not dedicate much of his time to this task, and therefore failed to achieve much. Therefore, the results of the activity of school-physicians were rather disappointing. In the first two decades of the 20th century, however, health conditions of school-children though only in more important towns were more judiciously supervised, and the number of physicians engaged in this work, increased rapidly.

In 1942, 40 per cent of the 530 000 pupils attending elementary schools had their health supervised by physicians engaged for this purpose while 13 per cent of the school-children did not come under medical control at all. The school-physician was assisted by a school-nurse who in 24 per cent of the pupils of elementary schools did whole-time work. As a rule, the schools

in towns employing a physician for health supervision, disposed also of a special school-nurse, whereas in country-towns it was the district nurse who acted in the capacity of school-nurse. For about a year past, the communities providing for health supervision in their schools by engaging the services of a school-physician, receive a State allowance, and the number of schools applying for this allowance is rapidly increasing. It is to be hoped that it will not be long before all Swedish school-children will have the benefit of this special health and school-hygiene supervising service.

Stockholm was the first town to appoint a physician in the capacity of school-physician-in-chief. Gothenburg was the next town to follow this example, and for about two years an expert in school-hygiene has been a member of the State Board of Education and acting as its whole-time State school-chief-physician. This medical officer is entrusted with the organization and establishment of health supervision in all Swedish Schools. Thus, this sphere of social science has received fresh impulses.

A trained and qualified personal familiar with the essentials of the care and rearing of infants and children is of valuable aid not only in promoting this branch of social science but also in enlightening the masses on child welfare. At all times mid-wives have been the first persons to whom mothers turned for advice. To the end of the 17th century, however, mid-wives lacked all the professional training and the necessary schooling to act as advisers. In the year 1682, a maternity home was established in Stockholm for the purpose of training mid-wives, and in 1697, the first manual of midwifery was published which also contained information on the care and fostering of infants. Not until the year 1921, however, were arrangements made for an organized training of mid-wives in the nursing and care of infants. Physicians trained in pediatrics conducted short courses in which the professional knowledge of mid-wives belonging to the older generation was brushed up. A few years later, a 2 years' training in midwifery including instruction in the care and fostering of children became compulsory. In addition, special classes were arranged at which mid-wives soliciting employment



at an infant welfare centre could obtain the necessary additional instruction in the care and rearing of infants and children.

The training of sick-nurses also included, though within certain limits, instruction in the care and rearing of children. Before the year 1923, however, no sick-nurses were available who were specially trained in both the care of healthy and sick children. Professor Jundell was the first to propose and establish a training school for children's sick-nurses. This school was founded by him in cooperation with Nordens Husmodersförbund (Society of Scandinavian Housewives) and was affiliated at the »Allmänna Barnhuset». Thanks to the efficiency of the nurses trained in this school, the sphere of activity of the different children's welfare institutions in Sweden could be rationally and successfully extended at a comparatively early stage. Without the valuable aid of these nurses the development of infant welfare centres as well as that of collective care of children in institutions could not have been so rapidly pushed forward to its present undoubtedly rather advanced stage.

In the year 1934 the State Training School for Children's Sick Nurses was established. It was affiliated to the »Allmänna Barnhuset» — now called Norrtull Hospital. The teaching and training within the frame of this school was based on the experience gained from the training school of Nordens Husmodersförbund which had been closed a few years previously. The curriculum of the State Training School for Sick Nurses includes a one year's course in the care and fostering of both healthy and sick infants and children. Sick-nurses who intend to solicit employment within the sphere of children's welfare work are supposed to attend this course. This school further offers facilities for an additional three months' training course for children's sick-nurses who wish to embrace a career within the province of social welfare of children.

Several homes for children arrange training classes in child care and fostering for those who want to become children's nurses. These classes extend over a period from 3 to 12 months. At some of these children's homes the training and teaching is satisfactory, at other it is somewhat inferior. So far, there do not yet exist



any regulations as to the scope, quality and duration of teaching and training of these nurses.

The present century has seen an increasing interest in children's welfare work in the form of providing for the care of children *outside their homes* in day-nurseries, play-schools, Kindergartens and similar institutions as *day-boarders*, a fact which in a high degree encouraged and furthered the activity in this sphere. Originally these institutions were private undertakings subsidized by either private persons or by philanthropic societies. Subsequently, the local authorities contributed to the cost of maintenance by granting subsidies, and for the past two years, these institutions were even subsidized by the State. The continuously increasing public furtherance of their activity resulted in a rapid development of this type of social children's welfare. Another contributory factor in this evolution is the fact that it has of late become more and more usual that both parents have an occupation necessitating their absence from home, and they must then leave their children in charge of others.

In 1941, there existed in Sweden 347 institutions designed for non-resident infants and children. Of these, 212 were day-nurseries. All the institutions together offered facilities for receiving 13 732 children. The majority of these institutions are supervised by a physician. The State subsidy to these charitable institutions is, amongst other things, conditioned on their providing for permanent health supervision. To the day-nurseries all children are admitted whose parents exercise a profession which prevents them from caring for their children in their home. For the care of the children at these institutions a certain fee per day is charged. Likewise, the play-schools admit all children between the ages from 3 to 6 years on payment of a small sum.

At the end of the 19th century the subject of the care and rearing of infants and children as *resident boarders* in charitable institutions or with private families was in the foreground of interest. This led to the establishment of a large number of children's homes. This form of child welfare is even in the present century a much discussed topic. These children's homes which were originally designed for more or less prolonged or

permanent care of infants and children, have, to a large extent, reorganized their activity. Nowadays, permanent or prolonged care of a child in an institution is not any longer considered the best alround providing for its welfare, as upbringing there does not favour its psychic development. This view even found expression in the Children's Welfare Law promulgated in the year 1924. Under this act it was recognized that if permanent or prolonged care and upbringing of children outside their home is required, boarding out with private families was the best manner available of providing for them. This new view regarding the care of children in institutions necessitated the reorganization of a large number of these. Some children's homes were closed down, and others provided for accommodation to receive children temporarily only. Generally speaking, all the children's homes which were established during the past decades were designed either for children in need of care for a short period outside their home, or for the observation of children in need of prolonged or permanent care, before boarding them out with private families. The »Allmänna Barnhuset» was among those institutions which reorganized their activity. In the years 1931 and 1932 it became an endowed institution which administered the returns of the funds of the »Allmänna Barnhuset», and used them for the benefit of child welfare work. Among other things, numerous reception homes for observation of the children are run with these funds. The buildings of the »Allmänna Barnhuset» have been concerted into a children's hospital, called Norrtull Hospital. To this hospital one of the two pediatric clinics of Stockholm is affiliated.

The new Children's Welfare Laws entailed another reorganization in regard to children's homes. Before these came into force, anybody could establish a children's home. No special licence was required. Generally speaking, its activity was not controlled, nor did the staff undergo any examination as to whether they were sufficiently trained and qualified for their tasks as welfare officers. The Children's Welfare Law of the year 1924, and the supplement to this law which followed in 1931, contain regulations to be observed by private persons in establishing a children's

home (licence), as well as directions as to the manner in which local authorities intending to establish a children's home should proceed, and in which its activity should be controlled. This year a new motion was submitted to the Riksdag intending: a) intensification of the control of the activity of the children's homes, b) stipulating that only children were to be admitted the familial circumstance of whom urgently called for protective care in a charitable institution, c) ensuring the best possible facilities for the care and upbringing of the children.

In the year 1940 there existed 281 children's homes providing housing accommodation for 6 200 children. About half of the institutions were maintained by foundations and private societies, and about one third by local authorities. 53 children's homes were designed for temporary care of children and an equally large number for permanent care. Among these, there were 7 children's homes designed for the care of such children who for some reason could not be boarded out with private families. If prolonged or permanent care of a child is intended, this type of children's home is, in fact, the only one, which in the light of the present criteria of the requirements for adequate care of the children, must be considered as fully satisfactory. 15 of the children's homes were designed for infants (accommodation available for 284 boarders), and 36 for mothers with their babies (offering facilities for 405 boarders). 4 homes are available for psychopathic children. In all these children's homes together 11 127 children were cared for in the year 1940. Almost all children's homes are controlled by a physician who, as a rule, visits these institutions from once to four times a month.

Under certain circumstances the State grants at the birth of a child to the mother a maximum subsidy of Sw. cr. 520 (at the birth of twins this is raised to 620 Sw. cr.). Part of this subsidy (110 to 120 Sw. cr.) is paid, irrespective of income or alleged needs, to the mother who is a beneficiary of sick insurance. If the mother is not insured against sickness, she receives a smaller sum (Sw. cr. 75) under the condition that her or her husband's yearly income does not exceed Sw. cr. 2 500. The larger part of the State subsidy (a maximum of Sw. cr. 400 and 500 at the

birth of twins) is paid after investigation into the individual circumstances. This grant is supposed to be used for the purpose stated by the mother, and to meet the pressing needs alleged to have arisen in conjunction with child-birth.

The following Table shows to what extent all these factors have influenced Infant Mortality during the past 200 years.

Year	1751/1780	1781/1810	1811/1840	1841/1870	1871/1900	1901/1930	1931/1935	1936/1940	1941	1942	1943
Infant Mortality rate pro mille . . .	207.5	198.2	172.5	146.0	114.0	70.9	50.1	41.9	37.0	29.1	28.6

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## **Some Extracts from Fredrik Theodor Berg's Autobiographical Memoranda.**

By

**FREDRIK BERG.**

On the 2nd of April 1845 Fredrik Theodor Berg was appointed by the Government to be holder of the new professorship at the Clinic for Children's Diseases attached to the Karolinska Medico-Surgical Institute, a post which had been instituted with the aid of a grant voted by the Riksdag in the preceding year, and on the 2nd of May 1845 he took up the clinical instruction at »Allmänna Barnhuset» (foundling hospital) where he had been appointed by the Government on the 21st of September 1842 to be head doctor and Director of the health and medical Service. On the 16th of November 1839, however, the directors of »Allmänna Barnhuset», at the proposal of one of their members, Dr Ahlberg, physician to the King<sup>1</sup>, had already appointed Berg to be »clinical medical officer» to that hospital. On this occasion Berg was abroad, and the sum granted by the directors was transmitted to him as a travelling allowance, in order to enable him, during his journey, to devote special attention to the hospital treatment of children. Not until his return from that journey in the autumn of 1841 did Berg learn that the decision of the directors involved not only a travelling allowance, but also an appointment as medical officer. An examination of the conditions in the hospital, however, immediately showed him that much remained to be done before the health and medical service there could be said to be at all satisfactorily organized, and still more before that institution could be considered suitable as a clinical school.

<sup>1</sup> Johan Daniel Ahlberg, b. 1793, d. 1856.

The enthusiasm and energy with which Berg tackled the task of completely reorganizing the medical service at »Barnhuset» and the stout resistance raised by the majority of its directors to radical reforms gave rise to a serious conflict, which was never completely settled during the time Berg was in service there. As regards an important question of organization which was perhaps the principal issue, namely the position of the medical officer responsible for the health and medical service relatively to the directorate and the other officials, Berg received strong support from the representatives of contemporary medical science, and posterity has confirmed the correctness of his views. The conflict at »Barnhuset» has attracted attention in recent years from various points of view; for the historian of clinical instruction in pediatrics its chief interest is that the external conditions for such instruction by no means corresponded to what the teacher considered essential.

F. T. Berg has left two series of autobiographical memoranda, specially intended for the surviving members of the family, and containing — besides reminiscences and personal experiences — a number of dry data regarding events in his life. Alongside of them, however, there are passages of more general interest, in view of the insight they give us into medical developments in this country.

In these notes the conflict at »Barnhuset» has naturally received a prominent place. In connection with the celebration of the centenary of the establishment of more systematic instruction in pediatrics, certain other pages of these notes seem to deserve publication. They throw light on his own education and his qualifications for the post of clinical instructor, whilst giving us some indication of the questions which had arisen in those early days regarding the organization of the clinical training of future doctors.

An orphan at an early date, Berg had to contend with financial embarrassments during his days of study. With the aid of earnings made by tutoring, eked out with loans, he was nevertheless able to complete his studies. In December 1830

at the age of twenty-four, he passed the »candidate of medicine» examination at Lund. On this subject he writes:

»I had pursued my medical studies with keen interest and diligence and had acquired a measure of knowledge which according to the requirement of the time seemed satisfactory. — — — In those days medical students had not the slightest inkling of practical medicine, as visits to hospitals never occurred. Whether I was well adapted or not for the vocation I had chosen I did not yet know, and to the heavy responsibility of the practitioner I had not yet devoted much thought. The knowledge required for that purpose would have to be picked up at Stockholm during the short time for which my remaining financial resources might suffice, and then the calling would be taken up as a *means of livelihood*. What could be picked up at Stockholm, however, was of little value for practical training.»

In January 1831 he entered upon his duties at Serafimer hospital under Israel af Ekström<sup>1</sup> and Carl Johan Ekström (ennobled as Ekströmer)<sup>2</sup>.

»Israel E. made his rounds very quickly without uttering a word of instruction or explanation regarding the diagnosis of the cases, but was generous enough in prescribing compound drugs. The so-called duties at the medical department consisted merely of bleeding and cupping, and he was not at all particular about the presence of the assistant doctors on duty. C. J. E. in the surgical department, on the other hand, was very particular not only about their attendance, but also about their uniform which — consisting of a blue apron, provided, in front of the chest, with pockets for the insertion of surgical instruments — must positively be worn, besides which a box containing first-aid requisites must be carried. Without giving any thorough clinical instruction, C. J. E. liked to explain and demonstrate, and this in such an entertaining and animating way as to afford good opportunity for learning; but none of us was permitted to try his hand at an operation. For my part, I by no means coveted that honour, having such a horror of the sanguinary and painful operations that I re-

<sup>1</sup> b. 1773, d. 1831. — <sup>2</sup> b. 1783, d. 1860. President of »Sundhetskolegium» (College of Health) 1849—60.



frained so far as possible from watching them. — No records were kept by those on duty, whose interest, at any rate in the medical department, was mainly concentrated on the collection of formulae for prescriptions.»

Towards the spring of 1831 Berg was compelled, for economic reasons, to take a post as medical officer at the canal works near Söderköping. This service lasted for more than half a year and was the young medical student's first practical work on his own account.

»During this appointment I soon learnt that it would not do to be always running to consult one's textbook in special pathology and therapy. I found it necessary to test matters myself, to individualize, collect and compare observations. This induced me to keep records, the zest for which afterwards remained with me throughout life, and in such an intense degree that I never found time to draw scientific conclusions from my records. My memory, by no means good by nature, seems to have been further impaired by lack of training and too much reliance on that hiding-place in the records.»

When Berg, in the autumn of 1831, with some small savings, returned to Lund he devoted much of his time to assisting a senior student named Zenius<sup>1</sup>, in arranging a »pharmaceutical institute» founded by the latter, with a collection of drugs, a library and a laboratory. His studies for the »licentiate of medicine» examination were thus delayed, and in the spring of 1832 his financial resources were again exhausted. An unexpected offer of a tutorship in a large estate in the south of Sweden was therefore readily accepted, as a makeshift. This engagement lasted no less than two and a half years and seems to have entailed a beneficial change for the poor, homeless student, though he himself afterwards considered that the time might have been better employed. On the 1st of June 1835 Berg passed the »licentiate of medicine» examination at Lund, and, after the termination of his clinical service at Stockholm, he obtained, on the 19th of November in the same year, the degree of Master of Surgery. Prospects of a readership in Anatomy had been held out by the faculty at Lund University,

<sup>1</sup> Johan Zenius, b. 1798, d. 1832.



and his mind was busily at work revolving plans for the organization of medical instruction, when he was proposed by Dr Thelning<sup>1</sup> as hospital doctor at Garnisonssjukhuset in Stockholm. After consultation with his patrons at Lund, he accepted the financially tempting offer.

»The main building at Garnisonssjukhuset had just been completed and was fully occupied by patients, when I took up my post. There remained, however, much to be done in regard to internal arrangements, still more in several of the other blocks, as well as with the embellishment of the place. My Chief, Thelning, lived for the completion of the establishment and well understood how to stimulate and turn to account the zeal which soon awoke in me to organize also the details of the medical treatment and instruction, so that they might bear good fruit. Thus, instructions for all details of the service as well as forms for reports etc., were drawn up; arrangements were made for collections of bandages, instruments and drugs, for regular meteorological observations as well as for the erection of premises for autopsy, and a chemicopathological laboratory; stringent order was introduced in the keeping of records of diseases and autopsies, and a library was founded, so that all aids for studies, so far as possible, should be accessible on the spot. Not one-fourth of this work would it have been possible for me to achieve without the support of Thelning. But I too was living at and for the Hospital, not passing beyond its pale for weeks. For a long time I superintended both the medical and the surgical department and was the sole Hospital doctor residing on the spot. Major epidemics of Typhoid Fever, Smallpox, Dysentery, Measles and Influenza during my term of office raised the number of patients to more than there had ever been before or since; but the more there was to do, the merrier. I vividly recollect that over the door of my study, I had inscribed Δός μοι πῶς. To find the sure startingpoint and standpoint was my aim. Quite a short time of practice on my own account had sufficed to convince me that the medical art, as then practised, was a blindman's-buff, all the more deplorable as it demoralized the doctor and brought

<sup>1</sup> Carl August Thelning, b. 1791, d. 1848, physician to the King.

the patient to the grave. To make the patient's body, so to say, transparent was the first essential; not until *objectum curationis* had been clearly viewed, ought there to be any question of intervening with any treatment. The physical method of examination and the diagnostics based thereon were known in this country merely by reputation, and to obtain any instruction therein was not possible. The need of its guidance for the numerous pulmonary diseases appeared indispensable. How I tried to grope my way on my own account and finally succeeded, is related in the report on the organization of medical treatment which I submitted in 1837 (p. 17).»

An extract from this report (p. 65), which was published in the first volume of »Hygiea», is given below: —

»A few months' experience had sufficiently convinced me that an indispensable need for the success of medical treatment at Garnisonssjukhuset was a reliable and rapid diagnosis of pulmonary diseases, partly because of the large number of such cases, partly in view of the rapid course of the inflammatory processes in strong fellows in their best age. The idea that it might be possible, by physical examination with percussion, auscultation etc, to gain the reliability in this respect which I had found it impossible to attain in any other way, induced me to make an attempt on my own account to acquire skill in this method of examination. I accordingly began, in the spring of 1836, to examine with a stethoscope the patients in regard to whom I presumed that the usual diagnosis had been most reliable, and where the specific sounds should be most distinct, and compared the lesions found in autopsy with the sounds I could hear. The numerous difficulties I encountered at first owing to all the false sounds, ignorance of the best procedure and places for the examination, and also from the opposition of the patient himself, etc, had wellnigh exhausted my patience, when my efforts had to be discontinued owing to a protracted typhoid fever. When I resumed my medical treatment in the autumn, I continued my studies with the stethoscope, which instrument I fancied was necessary for the perception of the auditory phenomena, and also had the satisfaction of having tolerably learnt to understand them.

Then in December came the Influenza epidemic with the daily admission of several cases of Pneumonia. The modicum of skill I had acquired in the use of the instrument proved insufficient, as the examination took more time than I could spare, as I had to divide my services among hundreds of patients. One day, dispirited and downhearted, I flung away the instrument, which, I thought, had cost me so much unrewarded trouble, and laid my ear direct to the patient's chest. What I had previously been able to hear with an effort and only when there was complete silence in the ward, I now heard easily and distinctly; the surface which had previously taken me a long time to examine, I could now survey in a few moments, at any rate in simple cases.

Thus I found, to my great gratification, that an advance had been made towards the fruitful use of auscultation for medical treatment on a large scale; for the merit of this method is little or none when it is merely employed, like a kind of »luxury article», for verifying what I had already got to know in another way, but, on the other hand, infinitely great, when it gives tangible certainty in regard to what in many cases I had not suspected, as it, so to speak, makes the chest well-nigh transparent, and thus in every disease can serve me with results, which often may be as important when they are merely negative as when they are positive. The trouble which is indeed entailed by the general use of the physical method of investigation in medical treatment will then be richly rewarded.»

The autobiographical memoranda continue:

»So far as I understood and the appliances of those days permitted, I tried to obtain enlightenment by examination of the patients' excretions. A series of investigations into the coagulation of the blood was facilitated by the »blood baths» entailed by the treatment of Pneumonia at that time. — — — Exact and complete hospital records were an essential element in this system of rendering the observation of the patient as thorough and complete as possible. Such observations could then serve as a basis for monographic compilations — — — Careful autopsies were necessary to complete the system, as they enabled me to rectify

any mistakes made in the records, which I had always first looked through. — — — Under these favourable conditions I had undoubtedly made a step forward, had obtained a firmer basis. This ought to have brought me a step forward also in the sphere of therapy — to a more 'expectative' treatment — but of this I cannot find much trace — neither I myself nor the times were ripe for this advance. On the contrary, I am inclined to think that physical diagnostics are at first liable to lead to overmuch medicamentous treatment.» — — —

»Convinced, by personal experience, of the deplorable state of things then prevailing namely that students who had not yet passed the 'candidate of medicine' examination were being appointed as Stipendiaries and Pensioners in the Army Medical Corps and were being sent out for independent medical practice, I realized the importance of the school which Garnisonssjukhuset was intended to constitute. What could be done in this respect would, of course, be greatly facilitated by the recent completion of the new hospital building.»

»During the great tension between the medical faculty of Upsala and the Karolinska Institute and owing to the high standard which Hwasser<sup>1</sup>, in some respects, had set up for the study of medicine, the view had gained ground that the 'candidate of medicine' examination must be passed before acceptance of permanent appointment or temporary service at Garnisonssjukhuset. The proposed agreement between Studiosi medicinae upsalienses involved questions of great weight. Would the number of dissectors at the Institute and of assistant doctors at Garnisonssjukhuset be thereby seriously reduced? Would the doctors of that Hospital be able, as superiors and medical officers, to hold their own against medicos who, with a high opinion of their own qualifications, might consider themselves unduly demeaned by the subordination and duties of assistant doctors?»

»I dreaded the ordeal which lay before me when in 1836 I had to receive several 'candidates of medicine' as assistant doctors, but I stood the test — — —. If I carried it through, it was thanks to

<sup>1</sup> Israel Hwasser, b. 1790, d. 1860. Professor of Medicine at Upsala 1830—1855. Sharply opposed the development of the Karolinska Institute into a complete medical college.

my own intense desire to learn from experience, to the rigorous control involved in record-keeping and autopsy, as well as to my successful efforts to employ percussion and auscultation as aids to diagnosis. Even before Huss<sup>1</sup> had returned from his travels in foreign countries, where he had acquired by training a far higher degree of skill, my assistant doctors had recognized the value of the schooling which they had thus received, though the amount of clerical labour with which they were saddled and to which the Hospital archives from those days, *if they are preserved*, should bear witness, seemed to them a heavy burden, and though, owing to the strict discipline I maintained, they may, perhaps, have considered me rather a martinet.»

»I recollect how Baron v. Weigel<sup>2</sup>, who had heard from Thelning that the method of auscultation had been adopted at the hospital, desired to test the reliability of the diagnosis, and, for that purpose, decided to attend an autopsy, where the diagnosis was hepatization of the inferior lobe of the right lung, and how, surprised by the result of the autopsy, he complimented us.»

Berg remained at Garnisonssjukhuset till the autumn of 1839, when, with the aid of a travelling bursary, he was enabled to make the previously mentioned journey of study in foreign countries. Owing to the interest of the directors of Barnhuset and their financial support, the study of children's diseases and of institutions for the care of children, became one of his principal objectives during the journey, which, for the same reason, was prolonged further than had been planned from the outset. It extended from October 1839 to July 1841; he passed through Germany, Austria, the north of Italy, Switzerland, France, Belgium and Holland, with longer stops in Berlin, Vienna and especially Paris. The official report of his travels (published in »Hygiea») contains detailed descriptions of a number of institutions for the care of children. Though the records of the journey in his autobiographical memoranda are rather summary, a few extracts from them will be quoted here: —

<sup>1</sup> Magnus Huss, b. 1807, d. 1890. Professor of Medicine at the Karolinska Institute 1846—60. President of »Sundhetskollegium» 1860—76. —

<sup>2</sup> Christian Ernfrid v. Weigel, b. 1776, d. 1848. President of »Sundhetskollegium» 1822—41.

»Rokitansky<sup>1</sup> and his young wife gave me a particularly friendly reception. I attended his lectures daily and was a frequent guest in his home. Numbers of corpses from Findelhaus (foundling hospital) lay piled up in a room adjoining his auditorium, without being dissected. I received his permission to study them, on the condition that I should show him if I found anything remarkable. I dissected hundreds of corpses, but without learning much, as I knew nothing about their preceding diseases. Findelhaus was managed without any scientific interest. Professor Berres<sup>2</sup>, who had carried capillary vessel injection to the highest perfection then attained, gave soirées for microscopic demonstration, with hydro-oxygen illumination. Here, in the company of Berres' assistants, the keen interest — which I carried home with me —, in microscopical examination was awakened. For medical practice at home this was still a novelty. Here, as in other matters, I did not get beyond an elementary stage, but wasted much time on my anatomical injections and other preparations.»

»My stay in Paris coincided with a remarkable period of advance in scientific research. Magendie<sup>3</sup> had based new physiological views on vivisections and Longet<sup>4</sup> further cultivated this field, Donné<sup>5</sup> gave microscopical courses, the Hungarian Jew Gruby<sup>6</sup>, a pupil of Berres in Vienne, had recently arrived in Paris, with far better training in the use of the microscope than Donné. With Gruby I entered into an agreement for the joint collection from the hospitals of objects for examination. Louis<sup>7</sup> had formed a little school, the members of which engaged strictly to apply the so-called 'méthode numérique', or objective statistical observations, consisting in complete records of diseases and postmortem reports, as a basis for positive knowledge. Physical diagnosis of pulmonary diseases had won fairly general application, and pathological anatomy was in good credit, at any rate for the confirmation of the diagnosis. Bouillaud<sup>8</sup> seems to have carried to

<sup>1</sup> Karl Rokitansky, b. 1804, d. 1872. — <sup>2</sup> Christian Joseph Berres, b. 1796, d. 1844. — <sup>3</sup> Francois Magendie, b. 1783, d. 1855. — <sup>4</sup> Francois Achille Longet, b. 1811, d. 1871. — <sup>5</sup> Alfred Donné, b. 1801, d. 1878. — <sup>6</sup> David Gruby, b. 1814, d. 1898. — <sup>7</sup> Pierre Charles Alexander Louis, b. 1787, d. 1872. — <sup>8</sup> Jean Baptiste Bouillaud, b. 1796, d. 1881.

extremes his theory of phlebotomy coup sur coup, and Piory<sup>1</sup> performed his tricks with the plessimeter in a rather charlatanic way, whilst the quiet Andral<sup>2</sup> gave full recognition to scientific testing and was just engaging the physicist Gavarret<sup>3</sup> as his assistant in blood investigations etc. Besides Guersant père<sup>4</sup>, the lively young Trousseau<sup>5</sup> joined the medical staff of Enfants malades and broke the red tape of the therapeutic treatment. Rillier<sup>6</sup> and Barthez<sup>7</sup>, perhaps Louis' most eminent pupils, were working there as internists.»

»At Enfants trouvés Baron senior<sup>8</sup> tried to show that he was at any rate not unfamiliar with auscultation, when he took up the babies and laid them to his ear, but what he could hear through their swaddling clothes must be left to our imagination. He often rushed past the cradle while prescribing something for a child who, as the nurses informed him, had already died. For the study of skin diseases there were good opportunities, and a Polish emigrant Matusinsky gave well-attended private courses. Ricord<sup>9</sup> was at the height of his reputation and was very entertaining and witty.»

»As at Garnisonssjukhuset I had been working in the direction desired by the adherents of 'la méthode numérique', I managed to get into close touch with the like-minded Frenchmen — — —»

During the above-mentioned cooperation with Gruby, Berg discovered the micro-organism which develops thrush in children. The first report on this discovery was given by Berg before the Swedish Medical Association in the autumn of 1841, and a thorough monograph on the subject »Om torsk hos barn» (in German translation »Über die Schwämmchen bei Kindern», Bremen 1848) was published in 1846. With regard to this treatise, C. Flensburg (Svenska Läkaresällskapets Handlingar 1916, vol. 42, number 3, p. 737) writes: —

»When we read Berg's classical treatise on thrush, we get the

<sup>1</sup> Pierre Adolphe Piory, b. 1794, d. 1879. — <sup>2</sup> Gabriel Andral, b. 1797, d. 1876. — <sup>3</sup> Louis Dominique Jules Gavarret, b. 1809, d. 1890. — <sup>4</sup> Louis Benoit Guersant, b. 1777, d. 1848. — <sup>5</sup> Armand Trousseau, b. 1801, d. 1867. — <sup>6</sup> Frédéric Rilliet, b. 1814, d. 1861. — <sup>7</sup> Antoine Charles Ernest Barthez, b. 1811, d. 1891. — <sup>8</sup> Jacques Francois Baron, b. 1782, d. 1849. — <sup>9</sup> Philippe Ricord, b. 1800, d. 1889.



impression rather of a quite modern essay than of a work written nearly three-fourths of a century ago. Berg in fact satisfies almost all that we rightly expect from a modern study of a parasitic disease; he strongly emphasizes that the microbe can be shown in all cases of the disease; he isolates and cultivates it, studies its growth in different nutrient fluids and its other biological characters, makes positive attempts at inoculation, describes in detail its appearance under the microscope, and, by observations of its reaction to different chemical solvents, places the therapy directed against the disease on a thoroughly reliable scientific basis. Berg's investigations all at once cast clear light on this previously so confused disease picture, and what later investigators have been able to add to his researches is quite insignificant.»

Berg's term of service as a teacher of pediatrics was not of long duration. From his office as head doctor he was granted leave of absence in April 1849, when, on the proposal of C. J. Ekströmer, he obtained a temporary appointment as Counsellor to the Medical Board, and his definite resignation was accepted in March 1851. At the same time Berg was elected on the directorate of Barnhuset. It was likewise Ekströmer's initiative that led to Berg's admission as a member of the Tables Archive Commission.<sup>1</sup> The first step had thus been taken towards the field of work to which he eventually came to devote all his energy, namely Sweden's official statistics. As from the spring term of 1855 he was granted leave of absence from his professorship of pediatrics and he definitively retired from that office in 1858, when his temporary post as Counsellor to the Medical Board was made permanent by Royal letters of appointment.

Berg's clinical lectures at »Barnhuset» were published in »Hygiea» in the course of the years 1847—1853. They were afterwards collected in book form under the title »Öfversigt af barnsjukdomarnas litteratur och svenska barnsjukvårdens historia» (Stockholm 1853).

In regard to his change-over from medicine to statistics, Berg

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<sup>1</sup> Founded in 1756. Stated to have been the oldest statistical office in the world.



has made a statement which may serve as a fitting conclusion to these gleanings from his autobiographical memoranda.

»Ever since my first term of service as a doctor, the statistical method, or the collection and grouping of observations, in order, by a total survey thereof, to be led on the way of truth, had indeed been my hobby, but the work I had now undertaken was, beyond comparison, more extensive and more arduous. The more this work engrossed me, the greater my admiration for the grand patriotic idea which had led to the foundation of our Tables Archive and for the men who, out of sheer love of their country, had maintained it. I became more and more imbued with such a feeling of reverence for my predecessors and their efforts, that I felt strongly impelled to preserve and develop the fruits of their zeal and labours. When I had managed to secure an office and archive room in the premises of the College of Health, and had there enjoyed the great pleasure I always felt in arranging the collections, I grew more and more fond of the work.»

»At the beginning of my service there, there occurred a sad event, which made such a deep impression upon me that it powerfully conduced to divert my interest from medicine to statistics. In the latter half of February (1854) H. R. H. the Hereditary Prince, Duke Carl Oscar Wilhelm Fredrik had contracted a catarrh of the lungs and on the 27th of February I was summoned to take part in his nursing. — — — I should have been prepared to ransom the Prince's life with any sacrifice, but on the 13th of March he passed away and, when I returned home, it was with the bitterest pain and shame at my own incapacity and that of the medical art. With ever-increasing and resistless force, the thought was borne in upon me that I ought to abandon the pursuit of a profession in which I had been so bitterly disappointed. Though this thought largely proceeded from an overweening pride, which had been deeply wounded on that sorrowful occasion, it had nevertheless a basis in a deeper conviction. My whole career as a doctor, and especially that part of it which had been devoted to the medical treatment of children, had incessantly increased my doubts as to the capacity of the medical art to intervene constructively in the treatment of the *disease*, with a clearly visualized

curative aim. I had realized, in increasing measure, that its true mission ought to be the warding-off of disease, the preservation of *health*. But to take a resolute plunge in the direction of this therapeutic scepticism, I had not found courage. This vacillation caused me perpetual qualms of conscience. Enough — the work at the Tables Archive was a welcome diversion and therefore all the dearer to me. Men and women reduced to figures were so peaceful and readily obeyed my orders for marshalling.»

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## **The Pediatric Clinics of the Universities and Medical Colleges as Main Centres of Medical and Medico-Social Pediatric Care, Research and Instruction.**

By

**I. JUNDELL.**

As late as the end of the nineteenth century children were still regarded, in many respects, as adults in miniature. This was one of the deeply-lying reasons why at that time the care of children, and especially that organized by the public authorities, still showed many serious deficiencies, even in the most advanced countries. This was one of the principal reasons why the then existing laws relating to children as well as the social and medico-social relief measures for their benefit had such a limited scope. It was also one of the chief reasons why the said laws and relief measures, which were largely modelled on conditions applicable to adults, were in many cases so unsatisfactory that, so far from redounding to the benefit of children, they actually conduced to their detriment.

The new century brought with it revolutionary changes in the above indicated situation. A stream of new and epoch-making discoveries, beginning towards the end of last century and continuously flowing, showed that childhood and the different stages of childhood in relation to one another are distinctive periods of life; and it also threw light on the deeper significance of this fact. These discoveries, most of which were made by pediatricists, have clearly indicated that legislation and relief measures in regard to children are bound to be more or less defective, or actually misguided, if we do not know, or fail to pay due regard to, the distinctive nature of childhood and its different stages.

It may seem to be a work of supererogation to remind our readers of the above indicated new investigations and discoveries and to stress their far-reaching importance. If I nevertheless venture to do so, it is because I shall confine myself to a concise survey of what seems to me essential as a background to the main tenor of this article.

It should be pointed out, to begin with, that the researches and discoveries to which the author has alluded relate especially to groups of diseases and abnormal states occurring with such frequency during the age of childhood that each of these disorders may be regarded as a serious endemic disease.

The manifold groups to which the author has referred include, for example, constitutional disorders in childhood, nutritional disorders in the different stages of childhood, the acute and chronic infectious diseases occurring during that period of life, the deficiency diseases of childhood and the allergic states. Moreover, in the course of the present century a number of important new results have been concurrently published in regard to the anatomy, biophysics and biochemistry of the different stages of childhood.

At least as important are the new researches regarding the psychology and psychopathology of the different stages of childhood, which have also led to new and animated discussions on the education of children at these stages.

The results of all these scientific labours involve immense progress in our knowledge of the origin of a number of different physical and mental diseases specially characteristic of childhood, their clinical disease pictures, treatment and prophylaxis.

A matter of far-reaching importance is that the new researches into the normal and pathological physical and mental states and courses during the different stages of childhood have given the doctors far greater facilities than before for diagnosing the very earliest and slightest manifestations of physical and mental deviations from what in those different stages is either normal or *desirable* in view of the dangers which modern culture — or lack of culture — involves especially for children. Thus in many cases it is now possible to diagnose borderline states between perfect

health and disease, or between certain or uncertain capacity to resist disease-breeding factors. Such diagnosis affords possibilities for rational prophylaxis against many widespread physical and mental diseases and abnormalities in the age of childhood. It gives us also inestimable facilities for therapeutic intervention at an early stage, and we all know that, if therapeutic measures are taken in due time, they are far more likely to result in speedy recovery.

The immense importance of the last-mentioned facts from hygienic, medical and economic points of view will be obvious to everybody.

So far, nothing has been mentioned that is not already known to doctors and especially to pediatricists. On the other hand, it seems to me that not even pediatricists have as yet fully realized some of the consequences to which the above reported facts must lead. One of the most important of these unconsidered consequences is that which is the real purport of the present article, which issues in recommendations to the following effect. That future pediatricists in particular, but also all medical students during their training should acquire greater theoretical and practical knowledge regarding (1) the normal physical and mental development and functions of children, (2) the clinical borderline states between perfect physical and mental health and marked pathological conditions and (3) all important prophylactic measures for the prevention of physical and mental diseases and abnormalities in children.

In accordance with the above, more exacting demands should be made in the first place in regard to the training of pediatricists and, to some extent, also the instruction of medical students in pediatrics. A matter of central importance is that pediatricists, who as a rule will presumably obtain appointments as head doctors in the children's clinics of provincial hospitals or those of the larger towns, and who will thus have a determining influence on the care of children in their respective localities, during their previous service as assistant doctors in university pediatric clinics should receive the best possible training.

The great discoveries made during the last forty years in the

field of practical medicine, and especially in pediatrics, have also entailed — or ought to have entailed — more exacting requirements in regard to the training of personnel engaged in the care and sick-nursing of children or in instruction in the care of children as a vocation: namely nurses and sick-nurses for children, child-nursing teachers, superintendents of homes for children, child-welfare inspectresses, etc. It is particularly important that all these groups should be required to show greater insight than heretofore into the psychology and psychopathology and education of children. Some knowledge regarding certain medical aspects of child psychology in normal and abnormal conditions should also be imparted to school teachers and, in some degree, also to jurists, especially judges.

Another lesson which has been brought home to us in the course of the present century is that a satisfactory physical and mental care of children cannot be attained without a vigorously conducted campaign of public enlightenment on these subjects.

The facts adduced above are intended to throw into clear relief the true significance of the proposals set forth below, which involve demands that the pediatric clinics of the universities and medical colleges shall be extended in such a way as to render them fully competent to discharge the various indicated duties.

If we proceed from the assumption that these pediatric clinics, as in fact is often, perhaps usually, the case, are equipped only with a ward for infants suffering from internal diseases and a corresponding ward for older children as well as with an outpatient department for such children, it seems evident that they should be eked out with certain special wards; and moreover that they should be linked up with certain medico-social institutions or homes already in existence, or planned, in the respective countries, although no representative of such institutions may have as yet been attached to them, for the purpose of pediatric research or instruction. Not until the above indicated extensions have been made, can these pediatric clinics be expected to serve as main centres for medical and medico-social pediatric research, care and instruction.

A specification of the wards and medico-social departments and homes with which the said pediatric clinics should be provided in order to serve as centres will be given further on (pp. 256—257).

The author does not consider it necessary to explain to pediatricists why these wards, departments or homes are required for the stated purpose, or how they are to be utilized for that purpose. The reasons adduced above should be quite sufficient. Though the said specification, as is only natural, proceeds primarily from the conditions in Sweden, this perhaps will not prevent it being noted also in other countries, or at any rate in certain medical colleges abroad. This specification, of course, includes only such wards and departments as seem to the author necessary in view of the present stage of medical and medico-social progress. The way in which future developments in Sweden and abroad may modify these requirements need not be discussed here.

Many will doubtless quite rightly urge that the proposed extensions of the said pediatric clinics could scarcely anywhere be carried into effect all at once. How long it may take before these desiderata can be realized in the different countries will largely depend on developments there in this field, and on the stage which pediatric instruction and research has reached at their medical colleges. It will also depend on the universities or medical colleges and their clinics and on the towns or districts where these institutions are located. The medico-social care of children in particular is generally under the charge of State or local authorities or the governing boards of private societies or foundations, which also control the organization, location and finances of their respective institutions. Where these clinics stand in good, amicable relations with the authorities and boards of the respective places or districts, it will be comparatively easy to bring about the said extensions: otherwise it will be difficult enough.

In certain countries, and especially in Sweden, the State, by itself establishing and managing such institutions, or by the grant of considerable subsidies in aid of their erection and maintenance, has placed them under firm control. In such circumstances, it

should be possible to carry the proposed extensions into effect without much difficulty, at any rate to judge by the great interest shown by the Swedish Government and Riksdag in national undertakings of this character. An intelligent interest in such cooperation has also as a rule been shown by the larger towns.

Owing to the circumstances 1) that the training of medical students in pediatrics has been obligatory from the year 1845 and has since then been closely associated with our oldest and largest institution for the care of children, namely »Barnhuset» (in the sequel called the Orphanage) in Stockholm and 2) that the author's efforts to organize in this country a pediatric clinic on the above indicated lines have been closely connected with his endeavours to effect a thorough reorganization of this institution, a brief review of its history may be of interest.

The Orphanage in Stockholm was founded in the year 1633 and opened in 1638. It had been preceded by the »Barna- och Tukthus» (Children's home and Penitentiary for adults) founded in Stockholm in 1624 by Gustavus Adolphus. This institution was a combination of a home for destitute children as well as for juvenile offenders in need of reformation and a house of correction where vagabonds, beggars, prostitutes and men and women with criminal tendencies were set to compulsory labour. The housing of children together with these debased adults had such deplorable consequences that this institution had to be closed after five years of existence. The increasing demand for the protection and care of older abandoned and neglected children obliged the Government to found an institution intended solely for that purpose. It was the above-mentioned Orphanage (also called the State Orphanage, »Kronobarnhuset»).

In 1786 the Orphanage and another home for children, namely the »Politibarnhus», were fused into a single institution. The last-mentioned home had been established by the authorities of Stockholm in the year 1756. In the course of the period from 1756 to 1786 it had firstly granted allowances to mothers or foster-parents in aid of some ten thousand infants and older children, and secondly had admitted 1 300—1 400 infants and children as boarders. More than fifty per cent of these boarders died during their stay there, and as regards the admitted *infants*, scarcely a single one had survived.

From the services of the Orphanage neither the State nor the children housed there had derived much benefit. In 1733 the Riksdag instructed a committee to inquire into its management. In the report of this committee it was stated: »In return for the many tons of gold which the State has invested in the Orphanage from the date of its foundation, it



has not produced a single useful member of the community...» But, in the course of the next fifty years there was no noticeable improvement in these conditions.

These grievous results of the relief work for children in those times were due to various reasons. The knowledge of the proper care and upbringing of children as well as the art of teaching were still on a comparatively low level; neither the teachers in this institution nor its other staff possessed the requisite training and qualifications; moreover, owing to lack of interest, they did not devote themselves to their duties as wholeheartedly as might have been expected of them even in those days.

Nowadays it seems utterly inconceivable that such things could happen in regard to children's welfare work. (The bad example of the above-mentioned »Barna- och Tuktohuset» did not deter the directors of the Orphanage, — which was solely intended for children's welfare —, in the years 1648—1757 from combining the Orphanage with a penitentiary for criminal adults and letting them work together with the children.) It was not only in Sweden, however, that most measures in this line failed to remedy the existing deficiencies. Other countries too reported similar experiences. But, in criticizing these failures, it should be borne in mind that it was not only the Government and local authorities, the managers, teachers and staff who were to blame. The fundamental causes of such conditions were the low level of medical science and hygiene in those days; the low state of pedagogics; the failure of the national communities fully to realize their social responsibilities; the lack of public enlightenment on the subject; and the primitive conditions of life in general. Hence all the attempts made to reorganize the institutions by new regulations failed to produce the desired effect, just as a better harvest could not be obtained merely by putting up a new fence round a tilled field.

The principal reason for the fusion between the Orphanage and Politibarnhus was the hope that, by the adoption of new principles, better results could be attained in regard to the care of the children. The adopted new rules were the following: Instead of being brought up for years within the walls of the Orphanage, the children were to be boarded in foster-homes, essentially in the country. Within the premises of the institute, chiefly infants were to be nursed, and that merely for a short space of time. Older children were to be nursed there only in cases where, owing to physical or mental disease, they could not be boarded out, or where for similar reasons, they had to be removed to the Orphanage wards from foster-homes. The institute at Stockholm would thus be mainly a *transit station* for the children, and the care and education of the children would be transferred to private foster-homes either in Stockholm or, more especially, in the country.

In this connection it should be observed that the Orphanage, which before 1786 had not admitted children under the age of six, after the said date received only such children; in course of time the admission of infants showed a great increase, whereas the number of admissions over the age of one year was successively reduced.

Since its opening in 1638 up to 1788, that is, immediately after its fusion with Politibarnhus, the Orphanage had received all children free of charge. In the last-mentioned year children were also admitted as Orphanage children *against a fixed sum*, determined by the governing board, the amount of which was gradually increased.

In 1788 wet nurses began to be engaged for the nursing and suckling of the infants. In 1800 it was expressly laid down in the Statutes of the Orphanage that the infants should be thus nursed and fed. Up to the year 1813 the nurse was not entitled to receive her own child at the Orphanage. After that date, however, she was permitted so to do, and was also entitled to have her own child admitted as an inmate of the Orphanage at a reduced fee, provided that for one year (after 1861 for 8 months) she had nursed and suckled another infant besides her own. In practice, this signified that the children of the wet nurses were received at the Orphanage in return for the nursing service of the mother. The proportion between infants and nurses was at first 3—4 infants per nurse. By 1814 this ratio had been reduced to  $1\frac{1}{2}$ —2, and during the following 25 years it averaged  $1\frac{1}{2}$ , a proportion which was afterwards maintained almost unchanged.

Infants admitted to the Orphanage, as already mentioned, were to be boarded out as soon as possible in foster-homes against a remuneration paid by the Orphanage until the child had reached the age of 14 years. After that time the obligations of the Orphanage towards the children ceased, and the entire responsibility for the children devolved on the foster-parents.

From 1785 to 1932, when the Orphanage practically ceased to serve as institution for the maintenance of children, it was managed mainly in accordance with the above indicated lines. During the first 27 years of this period the mortality among the children nursed in the infant wards of the Orphanage in Stockholm, according to Fredrik Theodor Berg's estimates, was so great that merely about half of the infants nursed there had survived. During the following 27 years, according to Berg, this mortality was reduced, the proportion of the infants who had died during their stay there being one-third. During the following part of the nineteenth century the mortality among the infants

was further reduced, though in a very irregular way: during the decade from 1891 to 1900 it varied between 6.1 and 17.5 per cent, averaging for that period 12.36 per cent.

In the summer of 1902 — I was then an assistant doctor at the Orphanage — I found, when skimming through the Directors' Report for 1900, that the figure for the mortality among the children nursed in the wards of the Orphanage at Stockholm was 8.4 per cent, whereas the corresponding figure for the *total* number of infants under the charge of the institution (those nursed in the infant wards at Stockholm and those boarded in foster-homes in the capital and the rural districts), to my great astonishment, was almost twice as high, namely 16.6 per cent. In order to convince himself on this subject, the author made a computation of his own for the three-years' period 1888 to 1890 and found the following: the average mortality among the children nursed in the infant wards was 12.84 per cent, whereas the corresponding figure for the *total* number of Orphanage infants was no less than 28.11 per cent; the mortality figure during the first year of life for the total number of children born in the country out of wedlock during the said three-years' period averaged 17.10 per cent. According as the figures of the Central Bureau of Statistics for the years 1891—1900 became available, they were also studied by the author. The figures subsequently published for the entire last-mentioned decade for the mortality during the first year of life among all the children (exclusive of still-births) born out of wedlock in this country showed a mortality of 16.62 per cent. The mortality for the *total* number of Orphanage infants during the same decade was no less than 20.95 per cent, whereas the corresponding figure for the infant-ward children, as above mentioned, was 12.36 per cent.

The most remarkable feature in the circumstances thus indicated was that nobody appears to have noticed or commented on the very marked differences — so significant for the results of the services of the Orphanage —, between the children nursed in the infant wards and those under the care of foster-homes.

Nor had it apparently occurred to anybody to compare the said figures from the Orphanage with the total mortality figures for the children born out of wedlock in this country.

As for the author these figures evoked not merely astonishment, but also long-continued reflection. For they told him plainly that among the Orphanage infants boarded out in foster-homes the mortality was so excessive that the general result of the Orphanage's activities was a sheer *loss* of lives; and that this charitable institution, instead of doing good, was actually doing downright harm. Although the maintenance of the Orphanage annually involved a considerable expenditure of public money, it would apparently have been better for the children if it never existed.

Besides the language so clearly spoken by the above figures, there is an important matter which does not seem to have been previously taken into account in this connection. Before the mortality figures for the total number of infants (exclusive of still-births) born in this country out of wedlock are compared with the mortality figures for the infants of the Orphanage, *they should be reduced by the mortality at any rate during the first week of life* (the «early mortality») or, more correctly, by the mortality during *the whole first month of life*.

The reason for this statement is that the Orphanage children — at any rate during the latter part of the nineteenth century and onwards —, on admission to that institution were almost always *at least* a week old. In most cases the age of these children was one to six weeks, a good many of them were two to three months old, and some of them still older. But the «early mortality» in Sweden at the beginning of the present century was so high that every fifth death among infants occurred in the first week of life, and that every third death among infants occurred in the first month of life. (In former days the mortality during the said earliest periods of life must certainly have been still higher.)

The above approximate figures for the mortality in the very earliest periods of life apply to the *total* number of children (exclusive of still-births) born in this country. There is, however, good reason to presume that corresponding data would show a

considerably *higher* mortality for children born out of wedlock. The mortality figures given by the directors of the Orphanage are thus most misleading, as, in view of the age of the Orphanage children, the excessive mortality during the earliest stages of life has been almost entirely left out of account.

It should moreover be noted that a child was never admitted to the Orphanage unless medical examination had shown that it was fairly normally developed and healthy, whereas the official mortality statistics for infants born in or out of wedlock naturally include all deaths among those children, with the exception of the still-born.

In short, the mortality figures reported by the Orphanage give a very distorted view, showing a great bias in favour of that institution.

The chief reason for the bad results attained in the Orphanage was no doubt the prematurely commenced and too rapidly effected weaning from breast-feeding. The time at which weaning was carried out was more or less determined by the need of vacancies for the admission of new children and by the number of applications at a certain time for the reception of infants as foster-children. It was supposed, and in those times there was also reason to suppose that everything was ordered for the best, provided that they did not discharge a child who was showing, or had recently shown, any of the then known marked signs of disease. At the beginning of the twentieth century we had as yet no distinct knowledge of the presence and significance of certain disturbances in infants — concealed or scarcely noticeable in the then clinical examination —, caused especially by noxious alimentary or infectious factors. In short, our doctors at the beginning of this century were still unable to diagnose intermediate states between complete health and evident disease.

An almost constant existence of such intermediate states among the infants nursed in the wards of the Orphanage was brought to light by my investigations made there at that time, namely during the years 1900—1902, regarding the day-and-night variations of the body temperature during the first year of life. These investigations, which were published in 1904, showed that

children nursed in large general wards, even if they appeared to be quite healthy at the ordinary clinical examination, were rarely in tiptop form. On the contrary, under such conditions, they are usually in some intermediate state between health and disease, setting in at short intervals and caused now by one, now by another noxious alimentary or infectious factor. This was doubtless the reason why, as the author learnt during his service as assistant doctor, so many of the children recently discharged from the infant wards had died either during actual conveyance to the foster-homes or after a few days' stay there. The immediate causes of the sudden deaths remained unknown, as inquiries never seem to have been made regarding the particular conditions and the symptoms in these cases. It may be presumed with great probability that, in many cases, the immediate causes of death were excessive heat during the long transports by rail, or the flaring up of some latent infection, or the aggravation of some nutritional disorder, or a combination of two or all of these factors. (Cf. the author's article in the work »I socialvårdens tjänst«).

The relief work of the Orphanage signified a systematic, and as a rule definitive, severance of the connection between mother and child. The same result, *i. e.* the separation of the child from the mother — and that too at a time when the babe should have continued to receive breast-feeding —, ensued from the measures taken by public authorities and private organizations when a distressed mother applied to them for relief for herself and her babe. The chief of these relief organizations, namely the local poor-relief boards, as a rule gave assistance in the following form. The child, in conformity with the mother's expressed desire, but not seldom contrary to her wish, was separated from the mother and placed in a foster-home; the poor-relief boards either paid the whole remuneration to the foster-parents or else caused the mother (sometimes, though more rarely, the father) to contribute to it to a larger or smaller extent.

Nor was regard paid to the welfare of the infants in the rather numerous cases where the parents, or some other near relation of the mother or father of the child were induced to receive the infant as a foster-child, whilst the mother was seeking

employment elsewhere. No more consideration to the child's good was taken, nor, as a rule, could be taken, when the mother, being unwilling to resort to the previously mentioned ways of assistance, had tried to manage for herself. In many of these cases the child was often weaned at an exceptionally early stage and was boarded out by the mother herself in some more or less suitable foster-home.

The results of these and, of course, also other factors, especially poverty and ignorance of the care of children, but sometimes also carelessness or actually deliberate neglect of the child, can be read in the high mortality figures shown by the official statistics for children born out of wedlock. At the beginning of the nineteenth century the Swedish mortality figure for infants born in wedlock was 18.30 %, as compared with 43.86 % for those born out of wedlock. In the eighteen-fifties the corresponding figures were 13.95 and 23.4, respectively, and at the end of the nineteenth century 9.38 as against 16.62.

Further light is cast on this subject by the statistical report, for the year 1894, of a Royal committee, showing the difference in mortality between children boarded out in foster-homes and other children. This report, which was published in 1897, reveals the following: — The mortality during the first year of life for all children born in Sweden (exclusive of still-births) was 10.88 %, but for foster-children no less than 28.08 %. In the age-group 1—7 years the mortality percentage among all the children in Sweden was 1.45 and among the foster-children 2.30. In the age-group 7—10 years the corresponding figures were 0.63 and 0.64 and in the age-group 10—15 years 0.34 and 0.39.

The above-stated and other conditions, observed at the same time or later, induced the author in the course of years to endeavour to bring about certain measures for improving the welfare of children and mothers in this country. Those which have a bearing on the proposed extensions of university pediatric clinics, as outlined in the specification on pp. 256—257, call for mention here.

A small newly formed society was advised in 1902, instead of a planned home for foster-children, to establish a home for mothers with



infants, with the object of providing accommodation and care for mothers and their infants during the whole normal lactation period. Even after discharge from this reception home, its managers should give them all possible assistance, but with the constant endeavour to maintain and, so far as possible, strengthen, the connection between mother and child. The first reception home of this kind was opened in Stockholm in January 1903 under the name of »Småbarnshemmet» (Home for small children).

The limitations, lack of insight, and confusion which at the beginning of the twentieth century often characterized the public care of children in this country led to a proposal drawn up by the author at the end of October 1906 for a rational organization of the care of children and maternity welfare throughout the country. This proposal was submitted in the form of a memorandum, dated 1st November 1906, to the Swedish Poor-Relief Association (Svenska Fattigvårdsförbundet), formed about a fortnight before at a meeting in Stockholm, although — or rather, just because —, the object of this association was stated only to be »to unite those who were working in poor relief and charity in concerted efforts for a development of relief work in accordance with the needs of the times».

In this memorandum, which in 1907 was printed under the title of »Barnavård och Modersskydd» (Care of Children and Maternity Welfare) in the first number of the new journal of the association. »Svenska fattigvårdsförbundets tidskrift», it was proposed:

That district centres for the care of children and maternity welfare should be organized in all parts of the country, with the following functions: to establish, within their respective areas, reception homes for mothers and infants; women towards the end of their pregnancy period should also be received in these homes, which might be linked up with suitable hospitals; to provide foster-homes for children who are to be boarded out; to supervise foster-homes; to establish homes for children, who for some reason, could not be boarded out; to provide guardians for the children; to establish advisory, information and assistance bureaux for mothers with children; to assist the mothers to protect their legal rights and those of their children; within their respective districts, to try and find all children and mothers in distress; to organize courses for women desirous of training in the care of children as a vocation; to organize courses of instruction in the care of children, especially for expectant mothers and possibly also for schoolgirls in the higher classes.

The functions of the district centres should be coordinated and guided by a head centre, which should also endeavour to obtain financial support from public monies in aid of their maintenance. By the publication of printed pamphlets as well as by the organization of lectures, the head centre should moreover try to arouse public interest in



questions relating to the care of children and maternity welfare. Furthermore, it should use its best endeavours to bring about amendments and extensions in the existing legislation on this subject.

A reception home for infants only was established in Stockholm at the beginning of 1912. It was called »Spädbarnshemmet» (Home for infants), and after some time was taken over by the Child Welfare Bureau of the Poor-Relief Association. In 1921 it was transferred to the municipality of Stockholm and was afterwards called »Spädbarnshemmet Eurenne-Ljungerantz' Minne». This home was intended firstly for infants who, for some reason, had never been breast-fed (or merely for a short time), and secondly for infants whose mothers, owing to sickness or other valid reason, could not, or should not, nurse or suckle their babes. Such children should be admitted to the Home for infants in case a suitable foster-home could not be procured for them, or if, in view of physical or mental disease, weakness or defect, too low age or required time of observation, they could not for the present be sent to a foster-home. In this way, and as the medical service in the home was under the charge of a responsible children's doctor, besides which the finances of the home were completely detached from the economic interests of private persons, this home for the reception of infants was the first rationally managed institution of this nature in the country, and an indispensable supplement to homes for mothers with their babes.

The services rendered by the said two types of homes in course of time received increasing appreciation, with the result that the local authorities in different parts of the country began to establish such homes. In the new Child Welfare Law of 1924 it was recommended that such reception homes should be established by the Children's Welfare Boards. In the report submitted in 1944 by the Government Committee on Social Care, it is proposed that it shall be incumbent on the Children's Welfare Boards to establish reception homes for mothers with infants as well as for infants without their mothers.

During the first twenty years of the present century, the medical and social care of children in this country was still greatly impeded by difficulties in finding persons possessing the necessary qualifications in this field. Even where a single special branch of this service, involving particularly arduous duties, was concerned, this was usually difficult enough. As for a nurse possessing a tolerably all-round training and competence in this line, such a person at that time could not be found at all. After several previous attempts, frustrated by opposition from various quarters, the author succeeded in 1923 in organizing at the Orphanage a two-year school for the training of well-qualified nurses and sick-nurses for children. The school was called »The Scandinavian Housewives' Association's Higher School for the Care and Sick-nursing of Children», the said association having given its assistance in the establishment and maintenance of the school. It soon became highly

appreciated for the valuable services rendered by the nurses trained there, in the field of medical and social care of children. In 1934 the school was reorganized as a State institution under the name of »Central-skola för utbildning av barnsjuksköterskor» (Central School for the training of children's sick-nurses).

In the above-mentioned memorandum to the Poor-Relief Association, stress was laid also on the desirability of enlightenment on the care of children for the general public, and more particularly for mothers and expectant mothers as well as for girls in the senior classes of the schools. A considerable time, however, elapsed before this proposal led to tangible results, owing to the lack of qualified teaching staff for practical and theoretical instruction on the subject. A start in this direction was made in 1914 with the assistance of a children's nurse, specially instructed and trained by the author for the indicated purpose and, with her assistance, the first »demonstration courses», intended for the general public, on the subject of the care of children were organized in the last-mentioned year. When a series of such courses had been held during the next time in different parts of the country, a request 1915 was addressed to the Swedish Poor-Relief Association to include such courses in its working programme. One year later, this proposal was adopted, with the result that the organization of these courses was very considerably extended. As from the year 1933 a considerable part of the expenditure thus involved was defrayed from State monies.

An essential condition for the organization of these demonstration courses on the required scale was the supply of a sufficient number of child-nursing teachers. A continuous and adequate supply of such teachers, in turn, presupposed the existence of a theoretically and practically well-trained corps of children's nurses and sick-nurses. A corps of that nature had been created by the above-mentioned higher school for the care and the sick-nursing of children. For pupils who had passed through that school, a three months' practical and theoretical continuation course for the training of superintendents of children's homes and of child-nursing teachers was organized in 1925. A certificate as a qualified child-nursing teacher was issued after careful selection among those who had passed through this course. Such certificates were granted only to pupils whose competence and personal qualifications for giving instruction in the care of children, and especially for conducting demonstration courses intended for the general public, had been thoroughly tested.

For the benefit of the pupils in the mentioned child-nursing school, but also for the instruction of medical students, a permanent child-nursing exhibition was arranged in the out-patient premises of the Orphanage in the year 1927. At certain times the exhibition was open also to the public. Moreover, part of the exhibition material was reproduced and combined into small ambulatory exhibitions, which by a child-nursing

teacher were demonstrated to the members of local courses and to the general public.

In order to facilitate the instruction of the pupils in the higher school of the Scandinavian Housewives' Association, but also to enable other persons interested in child-nursing work to acquire more thorough knowledge of this subject, a largish textbook, consisting of a theoretical and a practical part, was also published by the author. The effectivity of the demonstration courses was enhanced by the distribution of pamphlets or leaflets dealing with subjects connected with the course.

During the first twenty years or so of the present century the number of »problem» children and of nervous or other psychopathic children distinctly showed a steady increase. This led to the following proposals and measures.

In a short article in a small temporary journal, published in 1915, the author proposed the establishment of an institution for the observation, care and treatment of psychopathic children, which was also to serve for research and instruction regarding the psychology of children in normal and pathological conditions. In following articles it was urged that the pediatric university clinics should be provided with special departments for the said purposes. A proposal of the author to that effect, submitted to the second International Pediatric Congress at Stockholm in 1930, was adopted by a unanimous resolution. As a first step in this direction, the author had proposed that the clinic at the Orphanage should be equipped with such a department. These admonitions had aroused the interest of two persons known to the author, which induced them to give a large donation to Karolinska Institutet, as a basis for the establishment of such an institution at the pediatric clinic of the Orphanage.

In regard to the question as to the intervention of public authorities for the prevention and treatment of psychopathic conditions in children, an important step forward has now been taken in this country by the introduction this year of a Government Bill proposing State contributions for (1) facilities for the care of such children provided in the children's wards of central hospitals and (2) advisory bureaux for such children established by towns and counties.

The first information and advisory bureau for problem children and other psychopathic children and educational questions was opened by the author in 1925 in the out-patient department of the Orphanage.

The realization that a campaign against nervousness, psychopathy and demoralization in childhood was bound to be fruitless unless some insight into the mental care and upbringing of children under normal and pathological conditions was imparted to the parents and other persons responsible for the education of children, led to the following measures. Short lectures dealing with the elementary principles for the upbringing of infants and older children were introduced into the above-

mentioned demonstration courses for the general public. Proposals to the effect that the public should be afforded facilities for more thorough instruction on the bringing-up of children, by the organization of courses dealing solely with that subject, were afterwards submitted. These courses were to be conducted by women who, after the above-mentioned training as child-nursing teachers, by lengthy service in institutions for the care of children, and as social workers, had acquired more knowledge of child psychology and more experience of life.

The author's last proposal on this question was submitted at the fourth International Pediatric Congress in Rome in 1937 and was supported by a unanimously adopted resolution. It was to the effect that pediatricists, school doctors and other doctors, inclusive of medical officers who had had a lengthy experience as practitioners, should come forward as teachers of the parents, as »educators of the educators». The country should be divided into suitably delimited districts, and each such district at certain regular intervals should receive a visit from such a doctor, who should conduct suitably arranged courses regarding the psychology and bringing-up of children under normal and pathological conditions. Before the submittal of this proposal, the author for some years had held such courses for the general public in different parts of Sweden. The interest shown in them was very great. For the guidance of doctors who desired to conduct similar courses, the author drew up a detailed memorandum regarding the items suited for the course. For the benefit of practitioners who might desire to prepare themselves specially for such duties, facilities should be provided by arranging for questions relating to the psychology, psychopathology and upbringing of children to be included as a special subject in the comprehensive programme of the continuation courses for physicians.

The above data have been summarized here partly because they relate to arrangements which, in the author's opinion, should form parts of the pediatric head centres, partly because they briefly indicate the nature of those sections and their functions.

When the author in 1914 was appointed to be Professor of Pediatrics at Karolinska Institutet, and thereby also as head doctor at the Orphanage, he had, as indicated, long realized that the »services» rendered by the Orphanage were doing more harm than good. After serving for some time in this twofold capacity, the author soon became convinced that the Orphanage could be reconstructed into an extremely important, and indeed indispensable, institution for the whole country, by converting it into a pediatric clinic with the extended functions above indicated.

The first step in such a reconstruction of the Orphanage was to endeavour to organize wards there for sick infants and older children, as the existence of such wards — with which the Orphanage clinic was not then provided — is the most essential requirement for a pediatric clinic.

Sweden was the first country in the world where pediatrics received

During	Total number of Orphanage children at end of resp. years		Number of children admitted to Orphanage during resp. years				Out of the infants admitted during resp. years			
			Total number		Thereof infants		taken over against payment		nurses' children	
	min.	max.	min.	max.	min.	max.	min.	max.	min.	max.
1854 <sup>1</sup> -59	2425	2718	435	470	276	427	126	191	73	117
1860-69	2526	3860	529	807	380	756	153	333	113	184
1870-79	3246	3957	380	551	309	470	145	214	96	138
1880-89	2938	3310	365	439	269	445	139	259	89	111
1890-99	3356	4276	424	599	266	533	155	301	103	208
1900-09	4433	5932	554	710	433	592	220	345	186	220
1910-19	4037	5957	56	490	47	454	23	244	19	192
							Taken over and nurses' children			
1920-29	953	3652	4	38	1	34	1			
1930-35	61	711	0	6	0	3	0			

<sup>1</sup> »Additional children» (»Extra barn») began to be admitted to the Orphanage congenital weakness or the like, against a charge per day, paid by the child's parents. The admission of these children determined by the need of suitable cases for instruction for that purpose. — <sup>2</sup> The first year as from which annual reports were regularly submitted.

State recognition as a special branch of medicine. As far back as 1845 Government regulations were issued whereby training in pediatrics was made obligatory for all medical students, and a chair of pediatrics was established at Karolinska Institutet. As the first holder of this post the Government appointed Fredrik Theodor Berg, a man highly esteemed as a practitioner and scientist.

The material which Berg and all his successors as professors of pediatrics at Karolinska Institutet and head doctors at the Orphanage had at their disposal for imparting instruction in the pathology of childhood consisted mainly of the cases that occurred among the Orphanage infants during the time which elapsed between their admission to that institution and their discharge from it for reception in foster-homes. Up to about the last third part of the nineteenth century, the mortality among these infants, as already stated, was exceedingly large and the incidence of sickness among them correspondingly immense, so

Orphanage referred by police authorities	Average number of infants (including »additional children» <sup>1)</sup> nursed in infant wards during resp. years			Average duration, in days, of their stay there		Mortality per- centage among <i>Orphanage infants</i> (thus exclusive of »additional children» <sup>1)</sup> nursed in the infant wards		Mortality per- centage among total <i>Orphanage in- fants</i> (nursed in infant wards and foster-homes)		Number of »additional children» <sup>1</sup> admitted to infant wards during resp. years	
	min.	max.	min.	max.	min.	max.	min.	max.	min.	max.	min.
1870	110	79	109	64	93	20.0	37.9	20.0	30.0		
1871	197	83	163	53	78	14.9	25.6	13.1	23.0		
1872	136	74	147	51	88	10.0	34.6	10.0	38.0	25	60
1873	119	63	81	59	72	10.6	26.9	8.3	28.8	12	95
1874	205	84	198	64	115	6.1	17.5	14.2	33.1	73	135
1875	224	190	234	86	109	3.5	10.8	11.7	22.7	67	126
1876	197	29	216	97	122	1.17	6.55	6.3	13.6	35	121
Merely single infants under the charge of the Or- phanage	3	0	0	0	0	—	—			0	11
	0	0	0	0	0	—	—			0	0

1870. They were received for temporary medical treatment because of disease, gives. This medical attendance was thus not paid out of public monies, nor was the number of additional children was also too small to be of much value admitted.

that for some time ahead the material for instruction in the diseases of infancy was not inconsiderable. In consequence of the rapid development of medical science and hygiene during the last third of the nineteenth century, the mortality and sickness figures for the infants in question fell so low that the Orphanage clinic became ill-adapted for instruction in the diseases of infancy, the most important part of pediatric instruction. The facilities for such instruction were not improved by the increase in the number of infants in the wards, as the average time of treatment and the circulation among the sick infants were thereby reduced. These and other facts are illustrated by the accompanying Table 1, compiled by the author on the basis of the annual reports of the Orphanage.

The material of older sick children was also rather small, besides which it was lacking in variety and mobility. It consisted 1) of children over one year old who, in view of chronic disease, defective physical or

mental development or the like, could not be sent to foster-homes, 2) of older children who, for similar reasons, had been sent back from foster-homes to the institution in Stockholm. (Unlike the Orphanage Clinic, the second Pediatric Clinic of Karolinska Institutet, erected in 1882 and attached to Kronprinsessan Lovisa's Children's Hospital, disposed of a sufficient material of older sick children; but children under two years were not admitted there before the year 1933. In that year, on the initiative of Professor A. LICHTENSTEIN, a ward for sick infants was erected there.)

The pediatric instruction at the Orphanage was also affected by the effects of the Law of 1917, relating to children born out of wedlock, which entered into force in 1918. This Law revoked the Statute of 1778, whereby clergymen and midwives to whom unmarried mothers had applied were prohibited from betraying their anonymity. The Law of 1917 prevented also the parents of illegitimate children from remaining unknown, by prescribing that, if necessary, the parentage should be determined by legal inquiry and judgment. It also enacted that children born out of wedlock should receive from their parents such maintenance and education as corresponded to the economic resources and social position of the parents. (According to the regulations previously in force, it had merely been prescribed that children born out of wedlock should receive a sufficiency for subsistence.)

This new law entailed a catastrophic reduction in the number of children received at the Orphanage for future maintenance. In the nineteen-tens the number of newly admitted children was 490 as a maximum and 56 as a minimum. In the nineteen-twenties the corresponding figures were 38 and 4, respectively, and during the ten years immediately following, merely a few children, or none at all, were admitted to the Orphanage (see Table 1).

In view of these conditions, the author in 1917 submitted to the directorate of the Orphanage and to the teaching staff of Karolinska Institutet a memorial proposing that, out of the large number of vacant beds in the Orphanage, 45 should be reserved for such cases of disease among infants and older children *as would be suited for the pediatric instruction*. In spite of the stout resistance of the then directorate, this proposal in 1919 was carried into effect by the Riksdag, which voted a grant in aid of the costs in cases where neither the municipality of Stockholm nor any others were under obligation to defray them. The number of beds was gradually increased to 100. In addition, on the initiative of Professor A. WALLGREN and Dr N. H. HANSON, Director of the Stockholm hospitals, 40 beds intended for tuberculous children registered in Stockholm have been provided as from 1945 by the municipality of that city.

At the end of 1917 — with reference firstly to the above-mentioned Law of 1917, which in reality prohibited the anonymity under the cover



of which the Orphanage took over children against a lump-sum payment or against the wet-nurse service of the mother (see Table 1), thus definitely separating the children from their parents, and secondly to the fact that a Royal committee (of which the author was a member) was engaged in drafting proposals for new laws relating to children, and that these new laws would certainly necessitate a complete reorganization of the Orphanage —, the author proposed that the directorate of the Orphanage should request the Government to authorize the cessation of its then existing functions as from the 1st of January 1918. From that date and pending the entry into force of the expected new laws relating to children, the Orphanage should be provisionally organized as a home for mothers with infants. As such, however, it should be at the service only of mothers and children who had been remitted there by the child welfare boards, which should defray the actual costs of the Orphanage for their maintenance (inclusive of any costs for the boarding-out of the children in foster-homes). In other ways also, the child welfare boards were to retain their rights and obligations in respect of the children and their parents, who, on their part, were not to be exempted from the obligations devolving upon them in pursuance of the Law of 1917. This proposal, however, led to no result.

The out-patient department established in 1851, on Berg's initiative, in the old premises of the Orphanage was separated from this institution when it moved in 1885 into its newly built premises in Norrtullsgatan. The new buildings in fact lay in a then deserted quarter of the town, with bad communications, popularly called »Siberia». The out-patient department was therefore provisionally housed in rented premises, situated in the vicinity of the former Orphanage (at 70 Kungsgatan). In course of time, however, »Siberia» became a densely built quarter, with good communications. In view of this circumstance, and also because the Orphanage clinic often lacked cases suited for instruction, a request was submitted by the author in 1914 to the directorate for the reunion of the out-patient department with the Orphanage premises. The result of this request, which was several times repeated, was, however, negative; this, in spite of an offer to pay the rent, despite the fact that premises reserved for the out-patient department had been fitted up in connection with the erection of the new buildings and had since remained practically unused, and although the work at this department nowise encroached on or disturbed the activities of the Orphanage. It was not until 1921 that a renewed application on this matter led to a positive result.

From the year 1929 demonstration courses, specially intended for expectant mothers, have been held in the premises of this out-patient department. Moreover, one (later two) of the child welfare centres of Stockholm, on the initiative of Professor C. GYLLENSWÄRD, was attached in 1938 to this department and placed at the service of instruction.



In 1920 the author submitted to the directorate a proposal to the effect that the Orphanage should be reorganized as as central institution for *medical and medico-social* pediatric care, instruction and research, in which the prevention and cure of physical and mental diseases should receive an equal share of attention. The same proposal was repeated in 1921 and 1924 and, once more, in 1929. A detailed plan for the use of the Orphanage premises in case that the proposed reorganization was adopted was elaborated in 1923. All these proposals were substantially similar to that submitted by the author in the present article. The difference between them is that they have now been supplemented with certain additions and explanations, which naturally emanate from the leading idea as well as from the development of pediatrics and the medico-social care of children since 1929.

In the years 1929—1932 the activities of the Orphanage, as carried on since 1786, were completely wound up. For this winding-up two different proposals had been submitted, *viz.* firstly that of the directorate, and secondly the above-mentioned plans submitted by the author in 1920, 1924 and 1929, which had been unanimously approved by the teaching staff of Karolinska Institutet.

The proposal of the directorate was to the effect that the assets of the Orphanage should be mainly used (1) for the maintenance of temporary reception homes (*»upptagningshem»*) for children and (2) in aid of the provision of foster-homes for children who, after care and observation for some time in such reception homes, should be boarded out in suitable foster-homes, as well as for children in regard to whom such previous reception was unnecessary or could not be arranged. The said reception homes were to be of three different kinds, namely (1) homes for mothers with infants, where the mother and babe were to be together during the lactation period, (2) homes for infants without their mothers, and (3) homes for the care and observation of older children. Homes for the permanent care of children were to be debarred from such financial support. — Subsidies for the provision of foster-homes were to be granted to local authorities or child-welfare associations (*»barnavårdsförbund»*), to be used by them for the remuneration of delegates upon whom it devolved to find the best possible foster-homes for the boarding-out of children who could not be cared for in their own homes.

The author's proposal was to the effect that the assets of the Orphanage should be used primarily for the establishment of an institution for the medical and medico-social care of children, which should be utilized also for pediatric research and instruction, in accordance with the proposals made in the present article regarding university clinics as head centres of medical and medico-social pediatric care, research and instruction. The author's proposal was supported by the teaching staff of Karolinska Institutet and by the University Chancellor. The proposal of the directorate was nevertheless adopted by the Government.

It may be noted here, however, that in the 1944 report of the Government Committee on Social Services, it is proposed that the above-mentioned financial support *given by the Orphanage* in aid of the maintenance of reception homes and the provision of foster-homes for children *should be wound up*. The reasons adduced by the committee for this recommendation are similar to those given by the author in his criticism of the proposals submitted by the Orphanage directorate. This criticism was published *in extenso* in »Sveriges Landstings Tidskrift» in 1929.

In connection with the complete reorganization of the Orphanage in 1932, certain financial agreements were concluded between the State, as the supreme authority over the Orphanage, and the City of Stockholm. In accordance with these agreements, the Orphanage ceded to the City of Stockholm all the assets which were transferred to it when »Politibarnhuset» was fused with it, besides various other assets which were alleged to be the property of the City. Moreover, the Orphanage sold to the City its house property and sites in Stockholm, including the Orphanage buildings (with appertaining site) erected in 1885 in Norrtullsgatan, to which the institution had moved from its former premises erected in 1638.

This agreement was also to the effect that the Orphanage, out of the capital which it possessed after the said sales, ceded to the City of Stockholm a sum of 5 million kronor, to be used by the City for child welfare purposes. One million out of that sum was to be reserved for use by the City in aid of the erection of a new pediatric clinic for Karolinska Institutet; in the meantime its interest (50 000 kronor) was to be used for the maintenance of the existing pediatric clinic. The premises which, in accordance with the said agreement, had passed into the possession of the City, were adapted by it as a hospital, named Norrtull Hospital (Norrtulls sjukhus). At this hospital Berg's former clinic has been continuing its work pending the erection of a planned new building for the clinic, which is to form part of the new clinical hospital of Karolinska Institutet at Norrbacka near Stockholm.

Now that we have followed the development of our first pediatric clinic down to the present day, the reader may be asked to examine the following specification of the departments, homes, etc., with which a pediatric clinic attached to a university or a medical college, in accordance with the above, should be provided, and of the functions which should be discharged by such a clinic. Previously, however, the following observations should be noted.

Even if such a pediatric centre disposes of all the categories of clients mentioned in the specification (and possibly others as

well) and is provided with all the special premises and appliances required for the care and treatment of the children etc., as well as for research and instruction, such a centre, in itself, may nevertheless be compared with an otherwise highly developed organism, marred by certain defects which prevent it from functioning satisfactorily. In order that these head centres may function effectively, it is essential that they should form parts of a *central hospital*, which, in addition to the specified departments of the pediatric clinic, should be provided with clinics, out-patient departments and laboratories for at least the following branches of medicine: internal diseases, surgery, obstetrics and gynecology, diseases of the ear, roentgenology, pathological anatomy, serology and bacteriology. The existence also of other departments in the central hospital — such as departments for ophthalmology, orthopedics, neurology and psychiatry —, would also be of considerable advantage for the pediatric clinic. However, the need of immediate consultation with the last-mentioned departments is not so frequent or so urgent that the lack of them would appreciably impede the functioning of a pediatric head centre connected with the first-mentioned special departments.

*Specification of wards, departments, homes, etc., in, or connected with, head centres for medical and medico-social pediatric care, research and instruction.*

A. *Clinical departments etc.*: a) ward for sick infants; b) ward for older sick children; c) department for the observation and care of psychopathic children, or else a number of beds reserved for such children in ward b); d) department for chronically sick children (*e. g.* for children suffering from heart diseases in a chronic stage, severe chronic arthritic diseases, serious chronic diseases of the nervous system, severe skin diseases, certain psychoses and oligophrenias, severe disorders of the internal secretion, certain serious malformations, etc.); e) tuberculosis ward for children; f) convalescent ward for children; g) laboratories for scientific investigations and daily routine work; h) lecture hall. The laboratories and lecture hall should also be at the service, so far as required, of the medico-social sections.

Many pediatricists and other doctors would perhaps desire that these pediatric clinics should be provided also with a surgical department for children.

B. *Medico-social sections*: a) reception homes for breast-fed infants with their mothers; part of the premises of these homes should form a ward for expectant mothers; b) reception homes for infants without their mothers; also intended for certain Calmette vaccinated infants or infants who are to be subjected to the Calmette vaccination and who should therefore for some time be protected with special care against tuberculous infection; c) reception and observation homes for older children.

The children referred to under B a—c would, of course, in general be regarded, at the time of admission, as healthy children. In many cases however, they are not so, if the term »healthy» is given a strictly scientific definition. Many of these children, though they may not show manifest signs of disease, are nevertheless in those intermediate states between health and disease which, as previously pointed out, are so important for scientific research, early diagnosis, early treatment and rational prophylaxis. They are moreover, in many cases, in such a position that they are particularly exposed to external factors or influences which menace their physical and mental development.

C. *Out-patient departments etc.*: a) out-patient department for sick children; b) »child welfare centre», in the ordinary, restricted sense of the term; c) advisory bureau for psychopathic and other problem children; d) for demonstration courses of instruction in the care of children, for the general public; e) possibly, a care-of-children exhibition.

If we compare the above specification with the present situation at the hundred-years-old clinic, now called »The Pediatric Clinic of Karolinska Institutet at Norrktull Hospital» — setting aside the not yet existent, but certainly soon forthcoming, facilities for the care of psychopathic children — we shall find that this clinic still lacks the following: a convalescent ward for children, a ward for chronically sick children, a home for mothers with infants, a home for infants without their mothers,

as well as a reception and observation home for older children. With good will on the part of the authorities of the City and County of Stockholm (which already constitute the chief »reception areas» for the said pediatric clinic) it should be an easy matter to get the said wards and homes attached to this clinic. It may be added that both these authorities have always shown very good will towards Karolinska Institutet and its clinics.

In the above specification no figures are given for the number of beds that should be provided in the different wards or homes. Such figures have been deliberately omitted, because the number will depend partly on the need of accommodation for the different groups in a particular institution, partly on the size of the category of clients required for purposes of instruction; this size will obviously be affected by the nature of the clientele and by the number of persons to be instructed. In such circumstances the requirements in regard to the size of the different categories will show such marked variations that preliminary estimates could scarcely be of any value in drawing up plans for a contemplated pediatric clinic.

Still less will it be necessary to discuss here the building and location of the different departments and homes. It is obvious, however, that homes or departments which, for some reason, must be located at some distance from other homes or departments should not be placed so far from the main sections of the clinic, *i. e.* the clinic wards and out-patient departments, that medical examination, treatment and supervision is thereby impeded or delayed.

It may be asked why the above specification, which comprises wards, residential homes and out-patient departments, etc., contains no mention of such institutions as crèches, kindergartens, day homes for children, and so forth. As regards such institutions, it need only be stated that they should be easily accessible to the general public. If the pediatric clinic lies in a thickly populated place, it is, of course, all to the good that such institutions should be connected with the clinic.

Broadly speaking, the need of accommodation for a certain category of clients will doubtless depend on the size, density,

and kind of the population in the area provided for by the head centre. The »reception area» of that centre, of course, need not necessarily be equally large for all the different categories of clients. It is, for example, conceivable that the reception area of the same head centre for a particular group may comprise several counties, or perhaps even the whole country, whilst for another group it may be confined to quite a small district. Different demands will also be put forward according to the extent to which the need of institutions for a particular group has already been provided for within the respective districts. In no circumstances should there be any question of depriving a certain area of some institution which it really needs. All that is required is that — where this can be done without financial difficulties or other drawbacks —, one of the institutions intended for the care of a certain group of clients should be so located that it could be utilized with comparative ease also for research and instruction.

The chief consideration should be that the various important services relating to the care of children which involve medical treatment, supervision or guidance shall, to some extent, be represented at the institutions for pediatric instruction. This requirement should be set up also because the different groups, at any rate in some degree, should receive medical care that represents the acme of what our many excellent specialists in different branches can achieve when they are given facilities for systematic collaboration with one another. In this way we may obtain results which would perhaps otherwise be unattainable, and which will be of value not only for particular individuals and their families, but sometimes also for the nation at large.

The principal question with which the author has so far dealt is the supplementation of the *university* pediatric clinics with certain clinical departments, medico-social arrangements, outpatient departments, etc., which had hitherto been completely lacking, or had been represented merely by some particular group. In 1937, however, he also submitted proposals urging, for stated reasons, that it would be highly desirable, from all points of view, that every provincial central hospital which is already provided, or may subsequently be provided, with special wards

for children, should be extended substantially in the same way as is proposed above in regard to the university pediatric clinics. These provincial hospitals — possibly with isolated exceptions —, receive children from such a wide area as to permit of their being ranged in the same class of institutions as that represented by the university pediatric clinics. The fundamental difference between the medical and medico-social functions of these two groups of clinics lies in the wider scope, greater diversity and importance of the work carried on by the university clinics in regard to scientific research and instruction. In respect of actual medical treatment, on the other hand, there is no essential distinction. The author, however, desires expressly to emphasize that he by no means intends to convey the idea that the provincial hospitals should not participate in the said research and instruction. On the contrary, they should be given every possible facility for such participation.

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More detailed information regarding the investigations, proposals and measures mentioned in the above article can be obtained by interested persons from the author's previous publications in the following periodicals, annual reports and books.

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In regard to the Orphanage, its origin, development, legal and financial position, see the author's article »Översigt över barnavårdens historia i Sverige» (Survey of the history of the care of children in Sweden) in the Calendar of »Svenska Fattigvårds- och Barnavårdsförbundet» 1934 and 1939. As regards the reorganization of the Orphanage and the extension of Karolinska Institutet's pediatric clinic there, the reader is referred also to the memorials submitted by the author during the period 1914—1932 to the Directorate of the Orphanage and to the Teaching Staff of Karolinska Institutet.



## **Primary Tumours of the Optic Nerve and Their Relation to Recklinghausen's Disease.**

By

**INGVAR ALM.**

As early as 1893 GOLDMANN advanced the view that intraneural tumours of the optic nerve are but a part of an existing neurofibromatosis. In 1902, EMANUEL reported that most of the features of the tumours of the optic nerve were similar to those of tumours of the connective tissue of other nerves, and that there even was a similarity between these tumours and those of the central nervous system. In 1922, VOERHOFF claimed that they were a congenital lesion due to disturbance of the embryonal development of the neuroglia of the optic nerve. He was inclined to support the assumption that they were related to Recklinghausen's disease.

As regards the primary localisation of tumours of the optic nerve, the reader is referred to HUDSON's exhaustive paper (1912), LUNDBERG's thesis (1935) and DAVIS' monograph (1940). All these papers review exhaustively the cases of tumours of the optic nerve published in the literature. According to DAVIS, 300 cases of this disease had been reported in the literature up to 1940.

According to American reports, primary tumours of the optic nerve occurred in a material comprising more than one million cases treated at a clinic for diseases of the eye, in the ratio of 1 to 176 000 cases. LUNDBERG reported a ratio of 1 to 68 000 cases. In general, the following types of tumours occur: a) gliomas (most common in juveniles, in approximately two thirds of the cases), b) endotheliomas, c) fibromas (occurring rarely however).

The discussions as to the true nature of neurofibromatosis have recently again focussed interest on the problem as to whether there exists a relation between primary tumours of the optic nerve and Recklinghausen's disease. Generally speaking, two views have been advanced. VAROCAY, ANTONI, MASSON et al. expressed the view that they are localized to the sheath of Schwann. PENFIELD and YOUNG et al. claimed that they were localized to the nerve cells and axis-cylinders and subsidiarily cause proliferation of the surrounding supporting and protecting tissues. Histologically speaking, the optical nerve is a portion of the brain and is lacking the Schwann's sheath of the peripheral nerves. If evidence of the existence of a relation between Recklinghausen's disease and primary tumours of the optic nerve were available it would support the view advanced amongst others by PENFIELD and YOUNG.

The optic nerve is supposed to be made up of three types of neuroglial cells, i.e. astroglia, obligodendroglia and microglia (del Rio Hortega). The classification of tumours localized to this area is a much disputed subject. In 1932, del Rio Hortega described oligodendrocytomas of the optic nerve, and LUNDBERG, in accordance with del Rio Hortega's classification, grouped 9 of his 10 cases as oligodendrocytomas. DAVIS listed 3 of his 5 cases under the classification astrocytomas. The remaining 2 he considered to be cases of gliosis of the optic nerve. Del Rio Hortega (1928) reported that the oligodendroglia which constitutes 75 per cent of all glias corresponds to the sheath of Schwann of the peripheral nerves.

All 5 cases which came under DAVIS' observation manifested a mild type of peripheral Recklinghausen's disease (café-au-lait patches). In 4 of the instances of which 2 were brother and sister neurofibromatosis was hereditary. These findings led him to collect from the literature the cases of tumours of the optic nerve associated with Recklinghausen's disease. He found that 38 cases of this type had been published since 1873. In 12 of these neurofibromatosis was hereditary. He deduced from this fact that numerous tumours of the optic nerve were related to Recklinghausen's disease. Usually, however, the latter gives but

mild peripheral symptoms, and for that reason often escapes the attention of the examining oculist. It has been recognized for a long time that there seems to be a lack of consistency between the peripheral and central localization of Recklinghausen's disease. In cases manifesting numerous cutaneous tumours, the inner organs are less frequently involved. On the other hand, however, the reverse may happen. When establishing the antecedents little attention is paid to the hereditary instance as, frequently, the café-au-lait patches are the only obvious symptoms referable to a mild type of hereditary neurofibromatosis.

On the basis of the study of his own cases as well as of those from the literature, DAVIS assumed that the origin of the tumours may be classified in the following five stages: 1) At stage 1 there is a generalized hyperplasia of the neuroglia with astrocyte and obligodendrocyte formation. 2) At stage 2 there is hyperplasia of the arachnoid sequent to the tumour. 3) At stage 3 glial proliferation continues with extension of the growth to the arachnoidea through the pial sheath. 4) The gliomatous growth has destroyed the normal structure of the optic nerve and the surrounding tissues. 5) At stage 5 the tumour may show some characteristics of sarcoma.

Tumours of the optic nerve occur comparatively often in children. Out of the cases which LUNDBERG collected from the literature, and which were published during the years covering the period from 1912 to 1934, 59 were aged fifteen years or younger, and 37 were older than fifteen years. In 18 instances no information as to age was given. Out of the cases of primary tumours of the optic nerve associated with symptoms referable to neurofibromatosis which DAVIS collected, 19 were fifteen years old or younger, 18 were older, and in 1 case age was not reported.

As regards the heredity of neurofibromatosis RECKLINGHAUSEN expressed the view as early as 1882 that the disease could not merely be due to acquired properties, and THOMSEN in the year 1900 was the first to furnish evidence of the heredity of the affection. In 1918, PREISER and DAVENGOB furnished proof that the heredity was of dominant character and not sex-linked.

*Case Reports.*

*Case I.* Record no 689/42. An illegitimate girl, aged 2 years and 2 months, was admitted on July 7, 1942. Delivery by cesarean-section. Binovular twins. Birth weight 1 000 g. From April 18 to November 13, 1940, the child was in charge of the Kronprinsessan Lovisa Institution, Stockholm. She developed fairly satisfactorily. At the age of 7 months, her weight was 5 310 g. She was a cheerful baby and fond of playing with toys. She was cared for at several children's welfare institutions, and on June 29, 1942, she was admitted to the Infant's Home at Slagsta because of feeble-mindedness. She had already at that time a common cold. Her condition became worse and she was sent to Norrtull Hospital, Stockholm. On July 6, 1942, the date of her admission to this hospital, she was in a deplorable condition. She was small, cachectic, and weighed 7 270 g. Temperature 41°. She appeared listless, but reacted to external stimuli. The pharynx was appallingly reddened. Lungs: normal. As regards the inner organs there was nothing of note. Lumbar puncture revealed normal conditions. A few hours after her admission to the hospital the patient died. The post mortem revealed acute bronchitis but absence of bronchopneumonia. The optic nerve, especially on the left side, was considerably thicker than that of an adult individual. Orbita and eye normal. The brain weighed 1 050 g. Macroscopically it did not show any malformations.

*Pathologico-histological examination.* — The left optic nerve measured 7 mm in diameter, the right one 5 mm. The left optic nerve was sectioned after freezing. Frozen sections of the left optic nerve which were 200  $\mu$  thick revealed after staining (blood cell staining) that the left optic nerve contained several times as many blood vessels open to the circulation as the right one, and that the capillaries were grossly dilated. Cross-sections of the right optic nerve showed a coarse endoneurium. Transverse sections of the left optic nerve revealed a homogeneous picture. The stroma of the connective tissue was inconsiderable and delicate. The left optic nerve was obviously richer in cells than the right one. Judging by the silver-stained sections, this was principally due to proliferation of the microglia. There was absence of inflammatory alterations. Oxydase staining was negative.

Numerous sections of all portions of the brain were made. They did not show any macroscopic alterations. Pathologico-anatomical diagnosis: Gliosis of the left optic nerve (Lindgren).

The pathologico-histological findings, and the information that the mother of the patient had been operated on for a tumour of the spinal cord — this operation necessitated cesarean-section — led to an exhaustive investigation of the family history which revealed the following data.

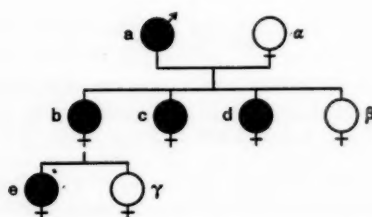


Fig. 11. The filled in circles indicate the presence of signs referable to neurofibromatosis.  $\beta$  dead at the age of 6 months of pericarditis,  $\gamma$  dead at partus (binovular twins).

a) The patient's grandfather on the mother's side manifested typical peripheral changes of Recklinghausen's disease. There were large cutaneous tumours disseminated about the whole body and the face.

b) The mother of the patient had been operated on in conjunction with the partus. There was presence of Séquard's paralysis. Extradural, pendiculated tumour on a level with the IX thoracic vertebra of the spinal column. *Diagnosis*: The tumour seemed to be something between a neurofibroma and a true neurinoma.

c) and d) Both sisters of the mother had café-au lait patches, chiefly localized to the groin.

e) The patient herself suffered from gliosis of the left optic nerve.

Three generations of this family had manifested different types of changes of Recklinghausen's disease. In the last offspring, a child aged 2 years, this was localized to the left optic nerve only.

*Case II* Record no 962/43. A boy from Dalarna, aged six years and 9 months, who was admitted on July 16, 1943. He was brought to the hospital by a person who lived in the neighbourhood of the boy's home during the summer, and had taken pity in him because his family was poorly off. The reason for his being taken to the hospital was that he manifested difficulty in speaking. No one but his own family was able to understand him. He had manifested exophthalmus of one eye since he was a baby. This had got worse as he grew up. For some years he even had a so-called fatty growth on his right thigh which recently had considerably increased in size. He was considered to be backward though he was bright and lively.

*General examination*: He was thin, and there were signs suggesting that the patient had previously had rickets. Pigmented café-au-lait patches of different size which were disseminated about the trunk (cp. fig. 12).



Fig. 12. The figures are taken at the same opportunity.

Pronounced right-sided exophthalmus. Above the crest of the right hipbone, there was an indistinctly outlined, comparatively soft tumour of the size of the palm of a child's hand. Apart from reduction in visual acuity of the right eye, the somatic and neurological examination did not reveal anything of note. He was very hard to understand and spoke with a typical Dalecarlien accent. Otherwise he was a bright and alert child. *Intelligence quotient*: Terman-Merill 79.

*Excision of the tumour and Pathologico-anatomical diagnosis*: The microscopical examination of the tumour on the hip revealed thickening of the nerves due to abundant newformation of connective tissue and Schwann's cells which caused splitting of the nerve fibrils. Presence of Recklinghausen's disease. (Bergstrand.)

*Examination of the ears*: Hearing normal. Ear, nose and throat conditions were normal.

*Examination of the eyes*: —  $S < \begin{matrix} 5/30 \\ 5/5 \end{matrix}$  (not improved by glasses).

*Right eye*: Compared with the left eye there was exophthalmus measuring

7 mm. Motion was normal. Pupils reacted normally. The fundi and the media of both eyes were normal. *Left eye:* normal (Berns).

*Roentgen examination:* Pelvis and hipjoints normal. Comparatively high and large skull, of normal structure and thickness. The anterior cranial grooves were short and the orbitae shallow. Neither bone destruction nor any other pathological alterations were demonstrable. There was no intracranial calcification. The optic foramens were larger than normal. In the films they measured on the right side 8 mm, and on the left side, 6 mm. They were of normal, round configuration. The orbitae were otherwise normally demarcated.

The patient left the hospital in good condition.

### Discussion and Summary.

In the first of the two cases reported in this paper, the pronouncedly dominant character of the heredity of the neurofibromatosis supported the view that the optic tumour was a part of this disease. In the second case there was presence of an optic tumour and Recklinghausen's disease which was verified by the pathologico-anatomical findings. Professor Henschen, who had the kindness to examine the preparations of the optic tumour obtained in the first case, expressed the view that the gliosis in this case was more likely a gliosis of the oligodendroglia type in accordance with del Rio de Ortega's classification. That it might be a case of oligodendrogliosis is quite in agreement with del Rio de Ortega's view, that the oligodendroglia which constitutes about 75 per cent of all glia and Schwann's cell are homologous (Bruderzellen). This again would support PENFIELD's view that the primary process in Recklinghausen's disease is localized to the nerve cells, and that this process causes a secondary process in the form of an irritation of the surrounding tissues (i. e. glia, meninges, endo-, peri- and epineurium as well as neurilemma, that is to say the sheath of Schwann) resulting in proliferation. An explanation is thereby furnished of the presence in some of the reported instances in one and the same patient of as many as 5 tumours all differing histologically and coexisting with Recklinghausen's disease.

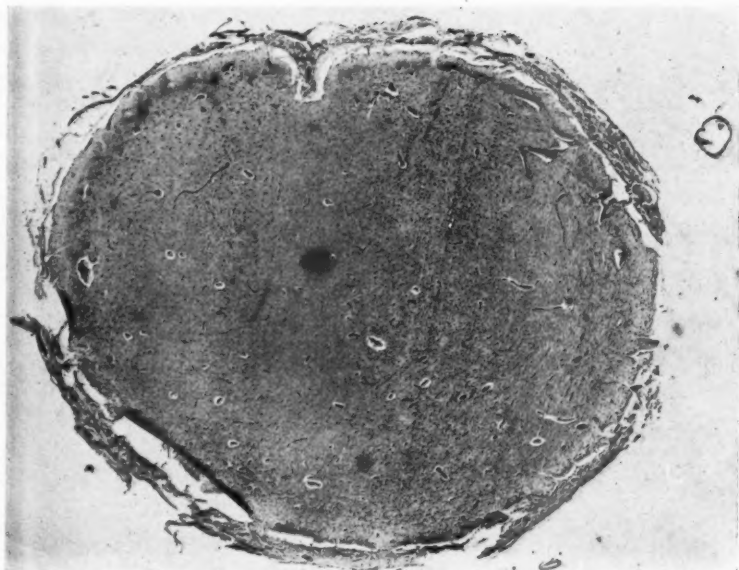


Fig. 1. Left optical nerve, (Van Gieson;  $\times 26$ ). Complete destruction of the normal structure.

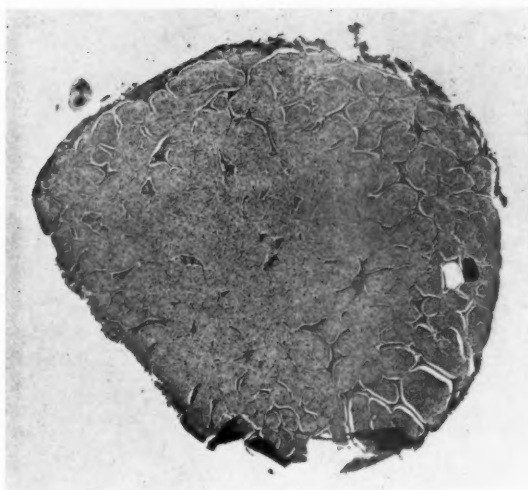


Fig. 2. Right optical nerve, (Van Gieson;  $\times 26$ ). Peripherally, the structure is partly maintained.



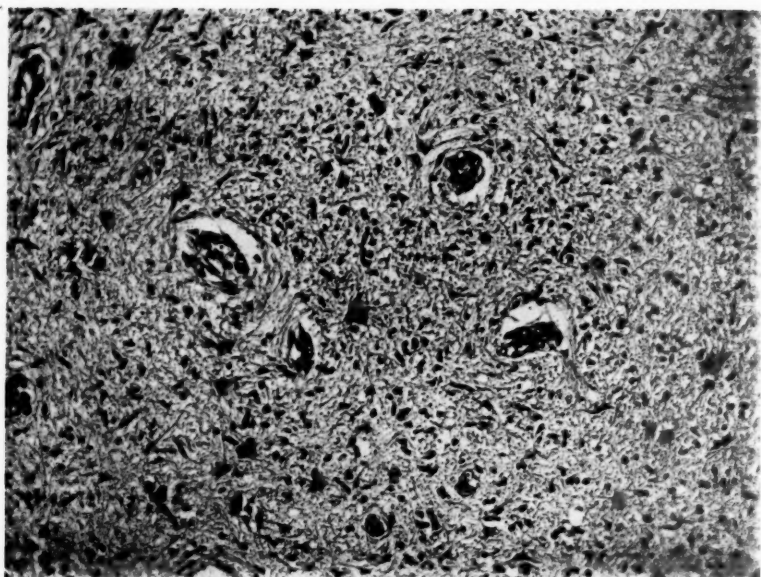


Fig. 4. Left optical nerve, (Van Gieson:  $\times 215$ ).

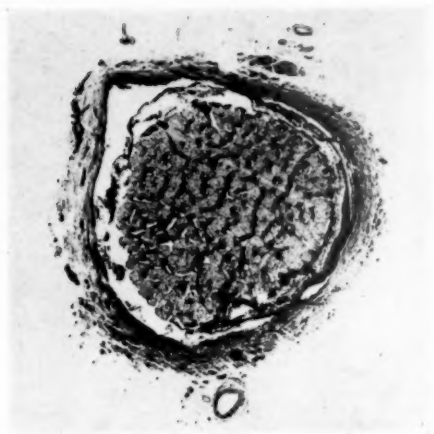


Fig. 3. Optical nerve of an adult, (the same  $\times$ ).

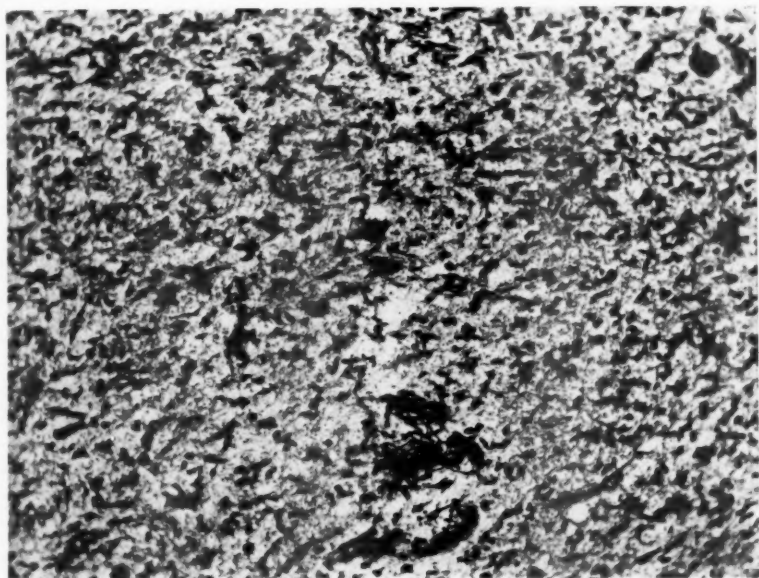


Fig. 5. Left optic nerve, (Penfield foot;  $\times$  216).

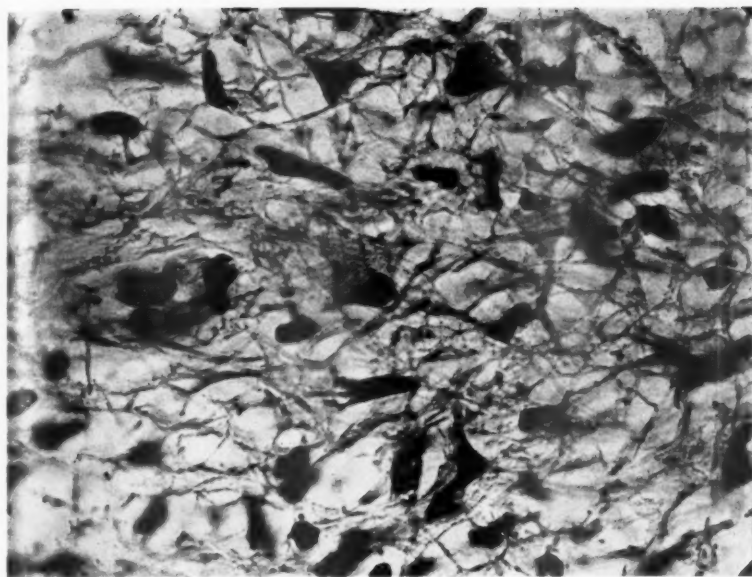


Fig. 6. Left optic nerve, (Van Gieson; Glia peripherally  $\times$  840).

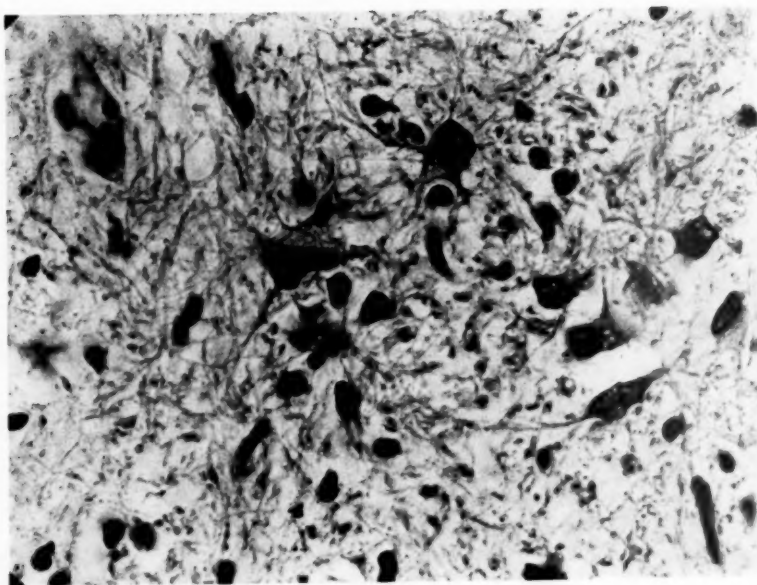


Fig. 7. Left optical nerve, (Van Gieson; Glia centrally  $\times 840$ ).

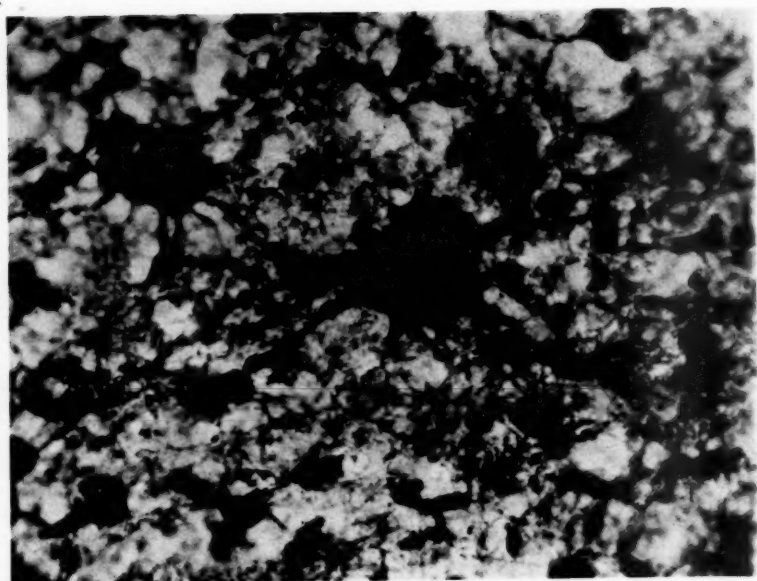


Fig. 8. Left optical nerve, (Glia, Penfield foot;  $\times 970$ )

Fig. 8. Left optical nerve, (Glia, Penfield foot;  $\times 970$ ).

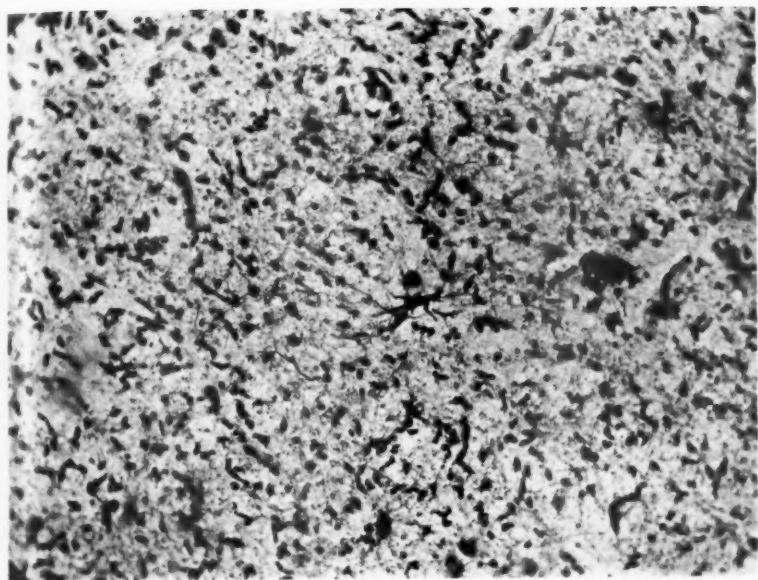


Fig. 7. Left optical nerve, (Van Gieson; Glia centrally  $\times 840$ ).

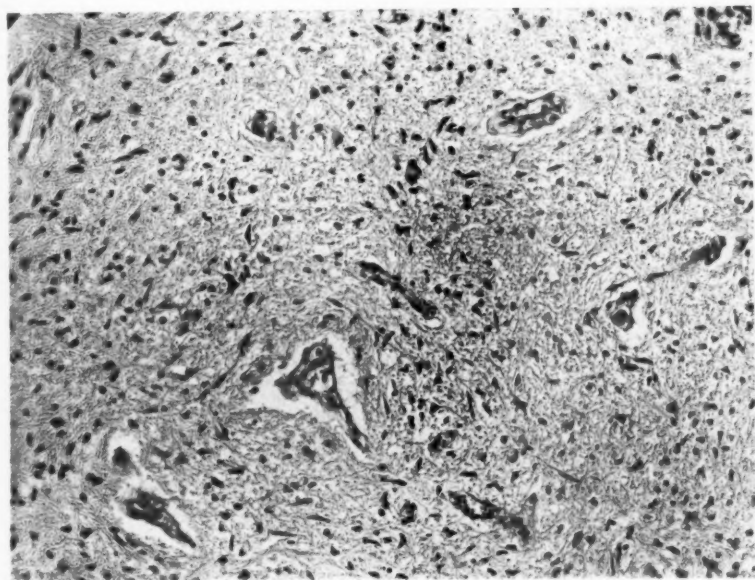
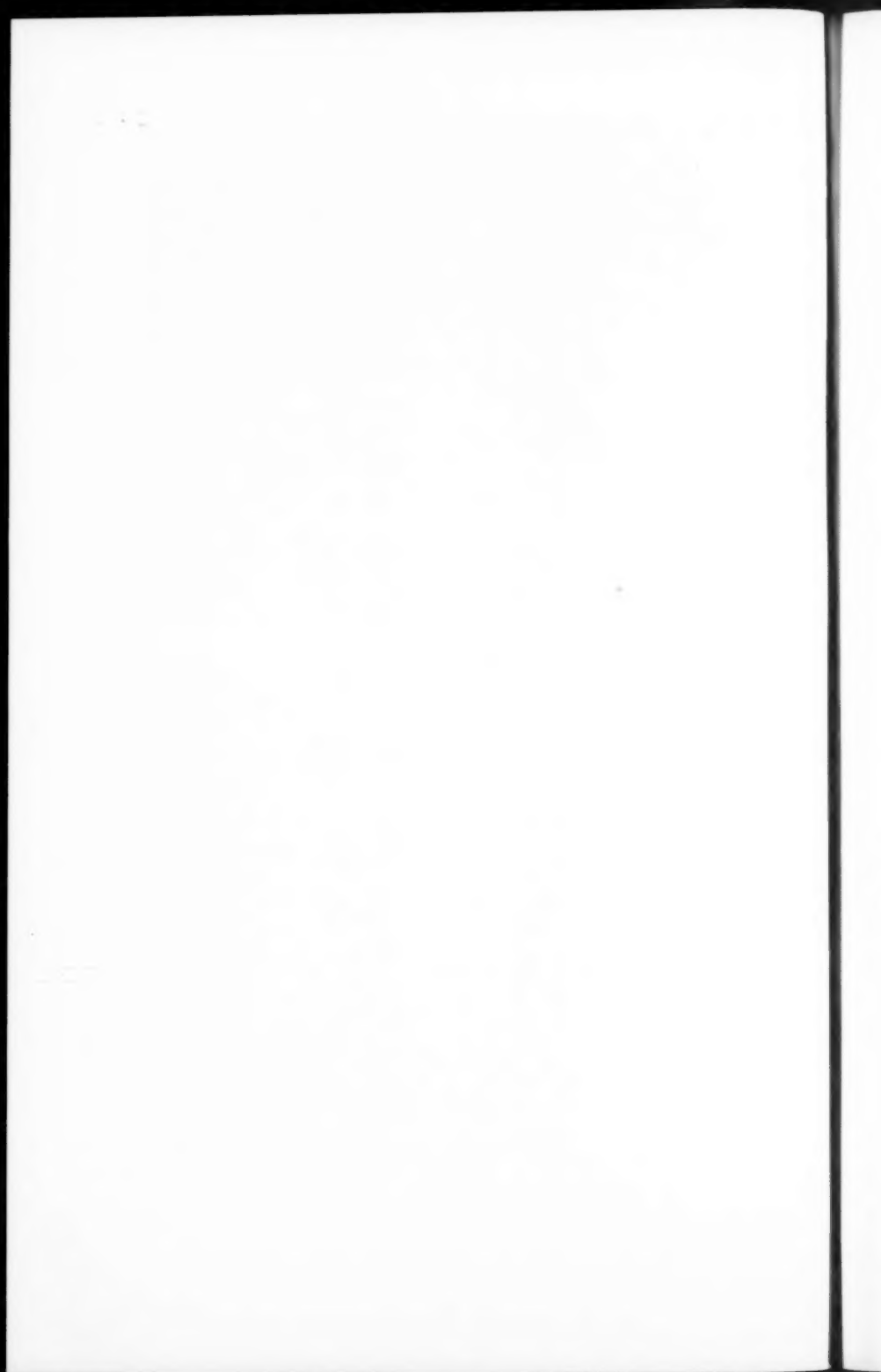


Fig. 10. Right optical nerve, (Penfield foot;  $\times 215$ ).

Fig. 9. Right optical nerve, (Van Gieson;  $\times 215$ ).



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## **Roentgenologic Determination of Heart Volume in Infants.<sup>1</sup>**

### **A Preliminary Report.**

By

**OLIVER AXÉN and JOHN LIND.**

Roentgenologic examination of the heart was for long been used merely to complement and control the clinical examination by percussion. The investigation was confined to studying the heart silhouette on anteroposterior roentgenograms from the stand-points of the morphology and topography, measuring its area and other representative measurements, and placing these in relation to expressions of the physical status such as, for instance, the height, the weight, and the width of the thorax. It was believed that conclusions as to the size of the heart could also be made from this examination. All these measurements, however, were made in one plane, and from the theoretical standpoint this method must be described as inadequate, seeing that the heart is a three-dimensional body. Reliable results can conceivably only be obtained if measurements are carried out in at least two planes at right angles to one another. It has been proved in practice, also, that the anteroposterior view of the heart silhouette cannot be used as a measure of the heart volume. The silhouette varies in shape and size even in one and the same individual under different conditions, and still less is it likely, therefore, that it will have the same size in different individuals. It has been proved, for instance, that hearts having the same volume can yield frontal silhouettes of different sizes, and vice versa, that hearts of dif-

<sup>1</sup> From a lecture read before the South Sweden Pediatric Society at Hålsingborg, December 1944.

ferent sizes can appear to be equal in size on anteroposterior views.

The first attempt at a determination of the heart volume was made by MORITZ in 1906. This investigator constructed a model of the heart from orthodiagrams taken in the frontal and sagittal planes, in other words, obtained by tracing over the heart as outlined on a fluorescent screen. PALMIERI (1920) and later LYSHOLM (1926) perfected this technique, which is regarded at the present time as being the most exact and the best method available. It is, however, too difficult and time-consuming for routine use.

In 1916, ROHRER worked out a formula for the calculation of the heart volume, and 16 years later KAHLSTORF (1932), without being aware of ROHRER's earlier publication, arrived at approximately the same formula in his calculations. The theoretical basis of both formulae is that the volume of a body is equal to the product of the size of its parallel projection — thus, as far as the heart is concerned, its frontal silhouette — and the average diameter of the body in the direction of the projection. The latter quantity has been found to stand in a constant relationship to the longest diameter of the body, which, in the case of the heart, is to be obtained from the lateral view. The value of the constant is dependent on the shape of the body.

KAHLSTORF regarded the heart as an ellipsoid for his volumetric determinations. He determined the frontal area of the heart planimetrically and multiplied it by the greatest depth of the heart in the lateral view and by the constant. JONSELL (1939) replaced planimetric measurement of the frontal heart shadow by a calculation using the formula for an ellipse, and demonstrated that in practice this simplification tallies well with the original formula. This also does away with the difficult task of sketching in the gaps in the contours of the heart at the top, and above all of those at its apex, where it is buried under the diaphragm shadow.

KAHLSTORF made use of orthodiagraphy when determining the heart area, a method which is not easy to apply in infants. Teleroentgenography, however, has been found to give approximately the same results as orthodiagraphy, although the



values are as a rule slightly smaller. In orthodiagraphy, the most lateral points are chosen on every contour. In teleroentgenography, if one attempts to take teleroentgenograms with an exposure time sufficiently long to ascertain the diastolic size of the heart the outlines often become indistinct for purposes of measurement. On the other hand, with short exposure times, the size of the heart will depend on which of the phases, systolic or diastolic, happens to have dominated at the moment of exposure. JONSELL, who studied the heart volume in both systolic and diastolic phases by the aid of a cathode ray oscillograph allowing exposure at a predetermined moment of the heart cycle, found in 9 cases a difference between diastolic and systolic volume amounting to 9—23 per cent of the diastolic value. He considered, however, that the difference in volume is generally very small. It is seldom, in fact, that the exposure happens to coincide with the climax of the systolic contraction, which constitutes only a small part of the cardiac cycle. Thus, double determinations made regardless of the cardiac phase show good agreement.

With teleroentgenography there is the advantage of being able to make the exposures in both frontal and sagittal directions at the same time. This makes it possible to obtain pictures of the heart in the same phase of the cardiac cycle, and also — a feature of even greater value — in the same respiratory phase. In adults, it has been demonstrated that slight alterations in volume take place in connection with breathing. When the pictures are being taken the patient should therefore be breathing easily and moderately deeply, and the moment of exposure should be at the end of the inspiratory phase when the heart shadow is most distinctly outlined against the background. In the case of infants, where the breathing is rapid and superficial, it is often difficult, however, to apply these rules.

Even in its normal state the heart varies in shape to such an extent that no mathematical formula seems capable of being applied to all cases with equal success as regards accurate measurements. For this result to be obtained it would be necessary for the heart to be a uniform, geometrically determinable body. It can be mentioned here that KAHLSTORF, in an endeavour to

ascertain possible errors in his method for determination of heart volume, took control measurements in human hearts hardened by formalin injection after death and then removed at autopsy. In 9 subjects with normal hearts and 3 with abnormal hearts he observed a maximum deviation of  $\pm 5$  per cent between the volume of the heart in question as determined by roentgenography and the actual displacement. Double determinations on living subjects yielded a maximum error not exceeding 15 per cent. Because of the observation that the heart volume increases with increasing length and weight but remains the same if the length alone is increased KAHLSTORF concluded that the weight of the body (within physiologic limits) decides the size of the heart and that the size is a linear function of the body-weight. In view of the fact that the basal metabolism and the circulation are more intimately connected with the body's area than with its weight (DU BOIS, GROLLMAN), NYLIN (1934) suggested that the heart volume should instead be correlated with the surface of the body. BJÖRCK (1944) examined in adults various correlation factors, viz. the height, the body-weight, the surface of the body calculated according to Du Bois' method, and the oxygen consumption per minute measured with the spirometer under standard conditions. He found that the height and the basal metabolism were unsuitable, and that the body-weight and the body surface showed approximately the same good positive correlation with the heart volume. In 1939, LILJESTRAND, LYSHOLM, NYLIN, and ZACHRISSON determined the heart volume through synchronous exposure in 2 planes at right angles in 100 healthy men between the ages of 21 and 47 and found values of 250—290 cc. per square meter of body surface. Double determinations in 10 cases yielded a figure of 4.7 per cent for the error regardless of the cardiac cycle. JONSELL obtained normal values of 250—450 cc. per square meter of body surface for adults in his large series of subjects.

There have been a great many reports on roentgen examinations of the heart in infants, but the results show many discrepancies. It has been asserted, also, that to obtain concordant values is almost impossible. The heart pulsations are rapid, and the breathing is quick, superficial and irregular. Further, the

base of the heart and the vessel shadow can hardly be distinguished with any degree of exactitude because the thymus shadow interposes. Because of the incomplete calcification of the skeleton the various features of the roentgenogram are not easy to distinguish. In view of all these circumstances roentgen examination of the infant heart is said to be difficult, and to a certain extent they furnish an explanation of why no satisfactorily established values are available with regard to the first two years of life. Earlier investigations show much individual variation even within the same age groups.

These previous investigations on infants will not be reviewed in this paper, since none of them pays regard to the heart as a three-dimensional body; they either use surface calculations as a basis or linear measurements in one plane. Two earlier investigations based on the method of calculation advocated by ROHRER and by KAHLSTORF will be briefly described, however.

LEHMKUHL, in 1929, published the results obtained from heart volume determinations in 100 children ranging in age from 0 to 14 years, 26 of them being under 1 year. The children were placed in the sitting position for the examination and ROHRER's formula was used for the calculations.

SAUER (1934) determined the heart volume by means of orthodiagraphy in 145 children, 51 of which were under 1 year of age. The examination was carried out with the children suspended vertically, and KAHLSTORF's formula was used for the calculations.

With respect to the infants under 1 year of age the results shown in the appended table were obtained. The figures within brackets denote the number of infants. In LEHMKUHL's investigations only the mean values were indicated. In SAUER's material all the values were included; from these the corresponding mean values have been calculated, the highest and lowest values being shown on the line below. None of the infants in SAUER's series was younger than 2 months. LEHMKUHL does not make any particular mention of the age.

LEHMKUHL mentioned that he determined the heart volume in a few cases before death and compared the result with that found at autopsy. The result was correct to within 10—15 per cent. For

	1st quarter	2nd quarter	2nd half year
LEHMKUHL . . . . .	54.3 cc (9)	70.8 cc (10)	69.7 cc (7)
SAUER . . . . .	51.6 » (7)	66.9 » (15)	85.4 » (27)
	31.9—62.6 cc	41.6—90.5 cc	53.0—121.0 cc

the rest no attempt was made in either of the investigations to determine the error of the method.

The investigation to be reported in this paper was made with a view to ascertaining the possibilities for determining the heart volume in infants by roentgenography. Although our studies are still in the experimental stage, since they form part of a more comprehensive investigation being carried out by one of the authors, some of the results already obtained will be described.

For the examination the infant is placed on its back with arms stretched above the head. The assistants also hold the patient's legs pressed against the underlying support. Low diaphragm arches are thus obtained, ensuring a good view of the thorax and the apex of the heart. As far as possible also, the lower outlines of the heart and the apex are projected free from the diaphragm. Frontal and lateral views are taken simultaneously and the examiner making the exposure stands beside the patient and is thus able to see that the picture is taken at a suitable moment. To obtain pictures of usable quality the exposure time must be as short as possible; in the present investigation it was 0.02 seconds. Electrocardiograms are made in order to establish which phase of the cardiac cycle is taking place at the time of the exposure. A photoelectric cell covered with a fluorescent screen is placed in the field of light and connected with the electrocardiograph (the 4th lead). By this means a mark is recorded on the electrocardiogram at the moment of exposure (fig. 1).

For both views the focal distance is 100 centimeters. In infants, the posterior contour of the heart in plain roentgenograms is not as a rule sufficiently distinct to allow direct measurements to be made. The patient is therefore given a teaspoonful of liquid contrast substance immediately prior to the taking of the films, so that the oesophagus, which follows the posterior contour of the

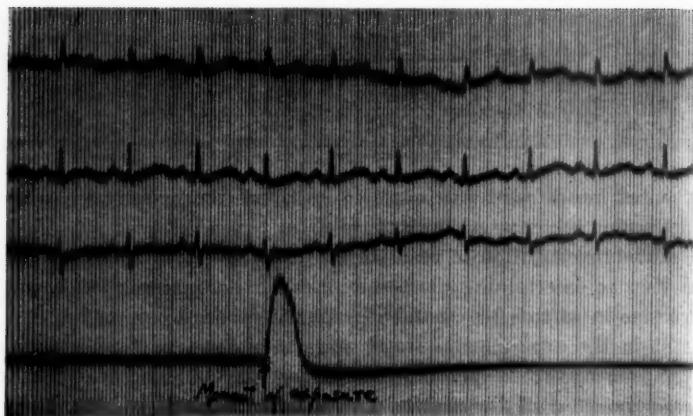


Fig. 1.

heart, will be visualized on the roentgenogram. By this means it is possible to make more exact measurements of the sagittal diameter of the heart. Thymus shadows which might place obstacles in the way of the measurements have not yet been encountered in our studies.

In making our measurements we make use of the method recommended by JONSELL; in other words, we calculate the area of the frontal heart shadow by the formula for an ellipse. The long diameter (l) is measured from the base of the vessel shadow on the right side of the heart to the apex. The broad diameter (b) is the smallest transverse line starting from the angle made by the heart and the liver, and the third measurement (d) is the greatest depth of the heart from the anterior edge of the moderately contrast-filled oesophagus to the anterior outline of the heart, if this is clearly visualized; if not, then to the posterior margin of the sternum. JONSELL has demonstrated that for practical purposes it does not matter if the axes obtained are not exactly at right angles to one another. The actual calculation is made by the KAHLSTORF formula as modified by JONSELL; this formula becomes, after simplification,  $k \cdot lbd$ . (See fig. 2 after JONSELL.)

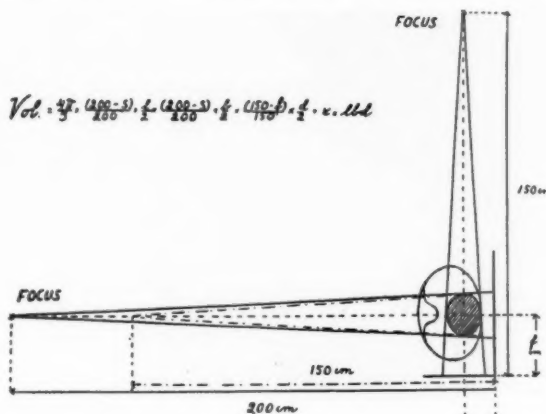


Fig. 2. Heart volume in  $\text{cm}^3 = (k \cdot l \cdot b \cdot d)$   
 where  $k$  = constant (incl. magnification factor)  
 $l$  = length in cm  
 $b$  = breadth in cm  
 $d$  = depth in cm.

One of the essentials for the making of heart volume determinations in infants is that both the centering of the roentgen ray tube and the position of the patient should be absolutely exact (fig. 3). It is necessary that an anteroposterior view without rotation of the thorax should be obtained; otherwise the heart silhouette will be distorted. If the patient is rotated even slightly to the right the long diameter of the heart will be shortened in the frontal view. If the patient is rotated towards the left the transverse diameter will be increased and the heart appear to be larger. The silhouette of the right side of the heart will furthermore be projected over the vertebral column and will no longer be clearly visualized. Exact adjustments are equally important for the lateral view, which must be taken in such a way that a pure lateral projection of the sternum is obtained. If this is not done, the position of the anterior contour of the heart will not be determinable.

With a view to discovering possible errors when the method is applied to children we made a few trial determinations on

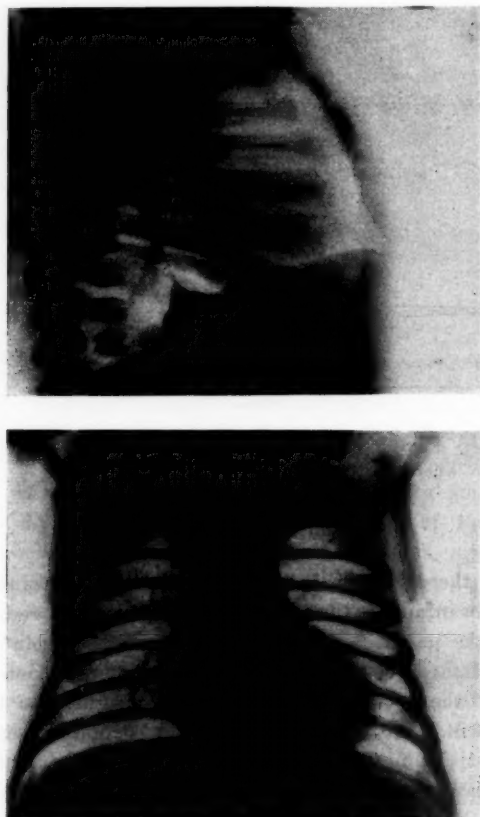


Fig. 3.

cadavers. Within one hour of the patient's death melted paraffin was injected into the ventricles of the heart. It was assumed that the atrioventricular valves would be insufficient after death and thus that the auricles would also be filled; our expectations in this respect were also fulfilled. The rapidly hardening paraffin would, we presumed, lessen the decrease in volume occurring when rigor mortis sets in. Roentgenograms of the heart were then made,

prior to autopsy. In order that the posterior border of the heart would be visualized on the lateral view a narrow sound was inserted in the oesophagus. Finally, the volume was determined at autopsy by measuring the displacement of the removed heart in a wide glass graduate. Before the heart was removed all the great vessels were ligated. The number of infants examined up to the present is 5 and the results obtained are presented in Table I.

*Table I.*

Heart volume determined roentgenologically after death (in cc)	Heart volume measured at autopsy (displacement) (in cc)
38	40
65	65
84	75
120	120
106	105

The agreement between the figures was surprisingly good, when we take into consideration the large sources of error inherent in the method which must be expected to apply in future investigations also. It must be said, however, that the preliminary results are encouraging.

The material of living infants consists of 45 cases, 26 boys and 19 girls, all with healthy hearts. Six of the infants were underdeveloped at birth and at the time of examination weighed less than 2500 g. The roentgenograms were taken in the morning, under identical conditions, with the infants calm (not crying) and fasting. In the following tables the material has been divided into boys and girls and arranged according to increasing length. (Tables II and III.)

In 18 infants double determinations were made by taking two roentgenograms in succession. As will be seen from the accompanying table (Table IV) the error of this method, calculated in



Table II.

Heart volume in 26 healthy boys.

Case	Age (days)	Weight (g)	Length (cm)	Heart volume	Heart vol./m <sup>2</sup>
1	9	1 725	42.5	32.5	239
2	44	2 330	46.0	29.0	177
3	49	2 330	46.0	27.4	168
4	13	2 790	48.0	29.7	163
5	37	2 150	49.5	35.2	209
6	26	3 000	49.5	39.1	204
7	26	2 250	51.0	24.8	139
8	7	3 300	52.0	44.5	212
9	41	3 840	52.0	52.9	237
10	71	4 500	52.0	65.6	276
11	16	3 800	53.0	46.4	206
12	39	3 550	54.0	40.8	185
13	49	4 050	55.0	40.8	171
14	42	4 100	55.5	60.6	253
15	62	4 800	57.0	56.2	213
16	48	4 780	58.0	59.4	224
17	69	4 850	58.0	52.8	237
18	79	5 150	59.0	57.4	205
19	129	6 345	61.0	71.2	224
20	81	6 175	63.0	88.2	282
21	219	6 300	63.0	57.1	178
22	203	8 450	68.0	100.0	266
23	229	7 800	70.5	98.0	261
24	365	8 460	72.0	133.0	338
25	365	9 100	73.0	127.0	305
26	365	8 800	74.0	127.0	304

the customary manner from the difference between the double determinations, is  $\pm 5$  per cent.<sup>1</sup>

<sup>1</sup> Our thanks are due to Docent L. GOLDBERG, of Karolinska Institutet, for his valuable assistance in working up the statistics in this paper.

Table III.

Heart volume in 19 healthy girls.

Case	Age (days)	Weight (g)	Length (cm)	Heart volume	Heart vol./m <sup>2</sup>
1	15	2 450	45.5	33.6	201
2	28	2 300	47.0	27.5	165
3	21	2 200	47.0	30.1	180
4	28	2 625	48.0	32.1	220
5	28	2 650	48.0	30.6	231
6	22	2 725	48.5	35.7	195
7	11	2 750	49.0	39.0	219
8	20	2 380	50.5	35.5	168
9	28	3 750	50.5	49.8	232
10	25	3 100	52.0	39.9	197
11	10	3 350	52.0	42.2	200
12	48	3 225	53.5	45.0	212
13	6	3 575	54.0	36.2	164
14	35	3 625	54.0	49.0	218
15	170	4 390	60.0	73.6	283
16	249	7 620	68.5	93.3	258
17	294	7 100	70.0	96.0	272
18	294	7 950	70.0	102.0	273
19	426	12 100	80.0	148.0	303

As has already been mentioned, in examinations on adult hearts the total heart volume has been correlated with different factors such as body-weight, body length, and body surface, and the correlation with body surface and body-weight has proved to be the best (BIÖRCK).

As there in previous determinations of infant heart volume, the volume has not been correlated with the infant's length, weight, and age it has been done in the present material. Finally, the heart volume per square metre of body surface area was also correlated with body length.

In fig. 4 the heart volume was correlated to body length. It is

Table 1V.

Double determinations of heart volume.

1st determination	2nd determination	Difference II—I	Mean	Difference in percent of mean
187	173	-14	180	- 7.7
176	178	+ 2	177	+ 1.1
228	210	-18	219	- 8.2
203	192	-11	197.5	- 5.6
195	229	+34	212	+16.0
154	174	+20	164	+12.2
214	244	+30	229	+13.1
171	171	0	171	0
289	277	-12	283	- 4.2
213	214	- 1	213.5	- 0.4
308	303	- 5	305.5	- 1.6
281	284	+ 3	282.2	+ 1.0
225	208	-17	216.5	- 7.8
262	255	- 7	258.5	- 2.7
306	300	- 6	303	- 1.9
310	299	-11	305.5	- 3.4
309	299	-10	304	- 3.2
335	342	+ 7	338.5	+ 2.0

 $n = 18.$ Mean difference in % =  $-0.07 \pm 1.67.$ Standard deviation of difference ( $\sigma_d$ ) in percent

$$\sigma_d = \pm 7.09.$$

Standard deviation of single determination ( $\sigma_x$ ) = percentual error of method  $\left(\frac{1}{\sqrt{2}} \cdot \sigma_d\right)$

$$\sigma_x = \pm 5.01 \text{ \%}.$$

clearly seen from the graph, that there exists a close relationship between these measurements.

No difference whatever was seen between boys and girls in this respect.

By current formulae (SNEDECOR 1938, BONNIER and TEDIN

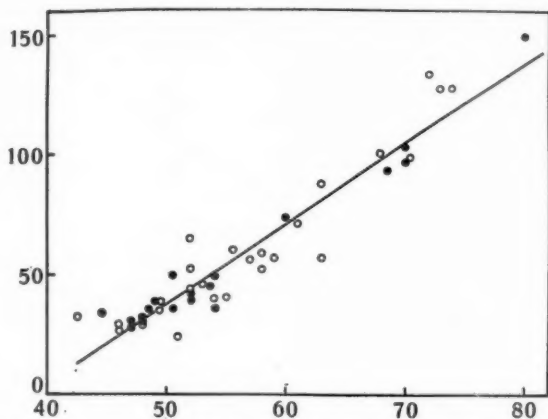


Fig. 4. Relation between heart volume and body length. (Formulae of regression line see table V.)  
○ boys, ● girls.

1940) the rectilinear regression line was computed from the values in Tables II and III (cf. Table V).

As the values for boys and girls completely coincided, the two sexes have been treated as one material in the following statistical calculations.

The correlation coefficient was  $0.95 \pm 0.01$ . This high correlation speaks in favour of the assumption that there really exists a rectilinear relationship between heart volume and body length at least for body lengths between 48 and 80 cm.

The relationship between the two factors investigated can also be demonstrated in another manner. By applying a regression line, the variation decreases considerably, if there is a close relationship. This gain can be expressed as the decrease in standard deviation according to the following formulae (2).

$$\text{Gain in percent} = \frac{\sigma_y - \sigma_{y-Y}}{\sigma_y} \times 100 \quad (2a)$$

where  $\sigma$  = standard deviation

$x$  =  $x$ -variate = found value

$y$  =  $y$ -variate = found value

$Y$  = a variate on the regression line = a value calculated

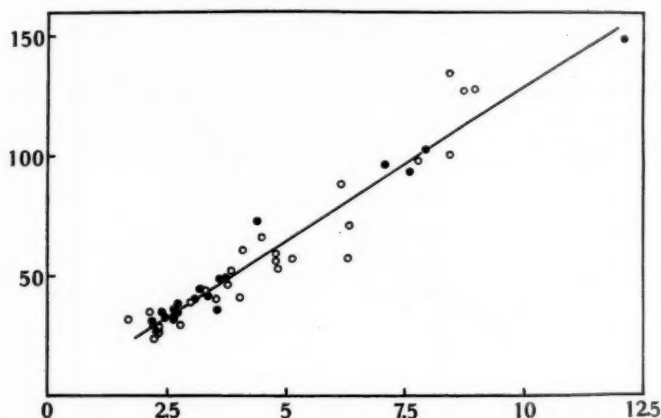


Fig. 5. Relation between heart volume and body weight. (Formulae of regression line see table V).  
○ boys, ● girls.

$$\text{and } \sigma_y = \sqrt{\frac{S(y - \bar{y})^2}{n - 1}} \quad (2b)$$

$$\sigma_{y-x} = \sqrt{\frac{S(y - \bar{y})^2 - \frac{(S(x - \bar{x})(y - \bar{y}))^2}{S(x - \bar{x})^2}}{n - 2}} \quad (2c)$$

where  $\bar{x}$  = mean of  $x$ -variates

$\bar{y}$  = mean of  $y$ -variates

$S( )$  = sum of ...

$n$  = number of variates.

The gain in this case was 70 % (Table V).

In fig. 5 the heart volume was plotted against body-weight. There seems to be a close rectilinear relationship.

The correlation coefficient was  $0.97 \pm 0.01$ . The close relation speaks in favour of the assumption that this relationship is rectilinear, at least for body-weights from 2.5–12.5 kg. The gain by regression was 74 %. (Table V.)

In fig. 6 the heart volume was plotted against age. There seems to be a close rectilinear relationship, the correlation

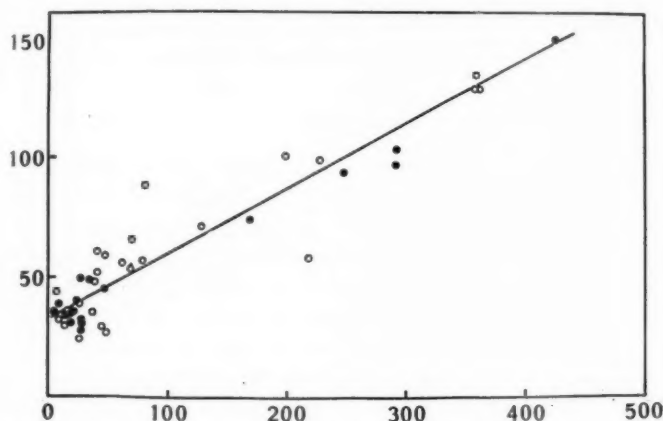


Fig. 6. Relation between heart volume and age. (Formulae of regression line see table V.)

○ boys, ● girls.

Table V.

Survey of relations.

Relation	Regression line	Correlation coefficient	Regression coefficient ( $y/x$ )	Gain by regression in percent
Heart Volume ( $y$ ) and Body Length ( $x$ )	$y = 3.32x - 128.28$	$0.95 \pm 0.01$	$3.32 \pm 0.16$	70 %
Heart Volume ( $y$ ) and Body Weight ( $x$ )	$y = 12.91x - 0.11$	$0.97 \pm 0.01$	$12.91 \pm 0.52$	74 %
Heart Volume ( $y$ ) and Age	$y = 0.26x + 32.61$	$0.97 \pm 0.01$	$0.26 \pm 0.02$	77 %
Heart Volume per $m^2$ ( $y$ ) and Body Length ( $x$ )	$y = 3.70x + 15.75$	$0.74 \pm 0.07$	$3.70 \pm 0.51$	32 %

coefficient being  $0.97 \pm 0.01$ . This is valid at least for ages between 9 days and 14 months. The gain by regression was 77 %.

In fig. 7 the heart volume per  $m^2$  body surface area was plotted against body length.

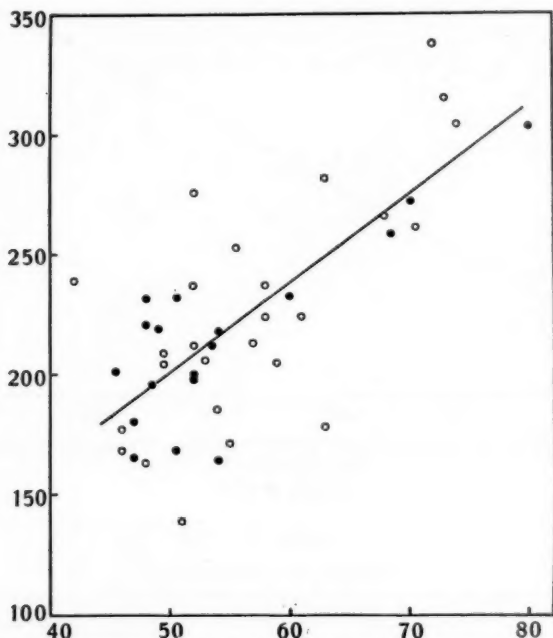


Fig. 7. Relation between heart volume per m<sup>2</sup> body surface area and body length. (Formulae of regression line see table V.)  
○ boys, ● girls.

The body surface area was computed from Du Bois' formula from 1927 and the nomogram according to the same formula.

There seems to be a relationship between these measures, but not of the same magnitude as those shown above. The correlation coefficient was  $0.74 \pm 0.07$ , and the gain by regression 32 %.

It cannot be concluded from these investigations whether the difference in relation between heart volume per m<sup>2</sup> body surface area and other measures as contrasted with heart volume (figs. 4—6) depends on deficiencies in the formulae used for computation of the body surface area in children or whether absolute heart volume is more closely related to other body measures. On the other hand, the close relationship between heart volume and body

length or body-weight in normal children points to the fact that it might be possible to distinguish pathologic cases.

### Summary.

Roentgenologic determination of the heart volume has been carried out in 45 infants with healthy hearts. The roentgenograms were taken simultaneously in two planes at right angles (the frontal and sagittal planes), and the volume calculated by Jonsell's modification of the Kahlstorf formula. In order to ascertain the error of the method a number of control examinations were made on cadavers, and in addition double determinations were made in 18 infants at the time of the roentgen examination. The absolute values for the heart volume were correlated with the body length and the body-weight and the heart volume per square metre of body surface with the body length.

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## On Acute Nicotine Poisoning.

By

STEN AXTRUP.

Acute poisoning, particularly of children, is at present a matter of immediate interest, especially in view of the rules incorporated into the Poisonous Drug Act on Nov. 26, 1943, according to which any person responsible for the poisoning from carelessness or neglect is liable to prosecution. The first item in § 12 runs:

It is incumbent on every person in the possession of poison without being licensed to trade in it

to keep the same in a suitable place in a strong and air-tight vessel or container or in a strong and tightly closed drawer or bag, well apart from goods intended for consumption,

under no circumstances to keep the poison in bottles of a kind customarily used for spirits, wine, malt beverages, milk or mineral waters, or in any other vessel (tumbler, cup, jug or the like) which on account of its common use might cause mistakes,

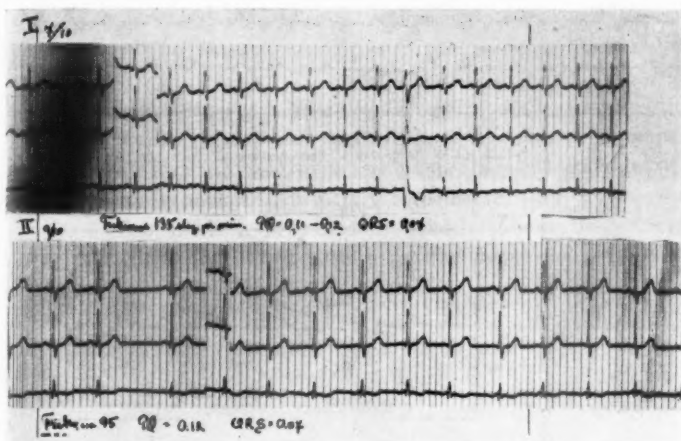
to ensure that the inscription on the poison wrapping is not removed, effaced or rendered illegible,

in all other ways to handle the poison with necessary caution, being particularly careful to see it is inaccessible to unauthorised persons.

The poisonings of special interest in this connection include those caused by nicotine, as substances with high nicotine content are often kept at home in places easily accessible to children. Nicotine poisoning in children is therefore not unusual. We have recently had a case of this kind at the Pediatric Clinic in Lund, which demonstrates the strong toxic effect of the nicotine in even

slight doses, particularly on the cardiovascular system, and which is an example in point of the careless way in which such poisons are often kept. The case is briefly reviewed here, but is more fully described in Sydsvenska Pediatriska Föreningens proceedings in *Nordisk Medicin* (in the press).

About 1 1/2 hours before admission to the Pediatric Clinic, the patient, a 3-year-old boy, had got hold of a bottle of concentrated nicotine solution intended for spraying fruit-trees. The bottle had been bought at a



Figs. 1 and 2.

drysalter's, and bore a label but no indications whatsoever that it was poisonous. As it had not been used, it had been put away on the floor in the attic of the patient's home. The patient had gone up there when no one was looking. He was found playing with the bottle, which he had succeeded in uncorking. He emphatically asserted that he had not drunk from the bottle, however, but had merely licked the cork a little. About 10 minutes later he began vomiting violently. He seemed giddy and wanted to lie down. He was taken in a taxi to the doctor, and then directly to the Pediatric Clinic. During the journey he vomited repeatedly. — On admission his stomach was immediately washed by gastric lavage. He seemed clear-headed and sensible and not particularly affected, possibly rather pale. His pupils were of normal size and mobile, and the other reflexes were normal. His pulse was rapid and ir-

regular, and the heart showed numerous extrasystoles, about one every third or every fourth beat. He came to hospital in the evening, and an electrocardiogram was taken next morning. The cardiogram (Fig. 1) shows a sinus tachycardia (135 beats/min.) and extrasystoles of supraventricular type. The T waves in lead III are weakly negative.

A new electrocardiogram was taken two days later (Fig. 2). Here the patient showed a sinus arrhythmia recalling a respiratory arrhythmia,

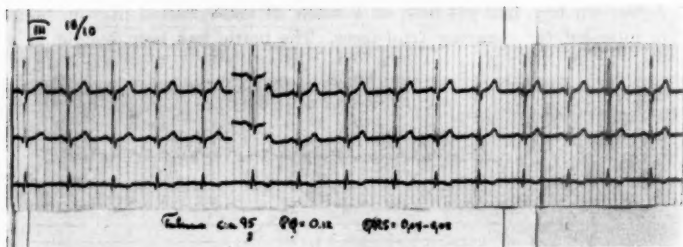


Fig. 3.

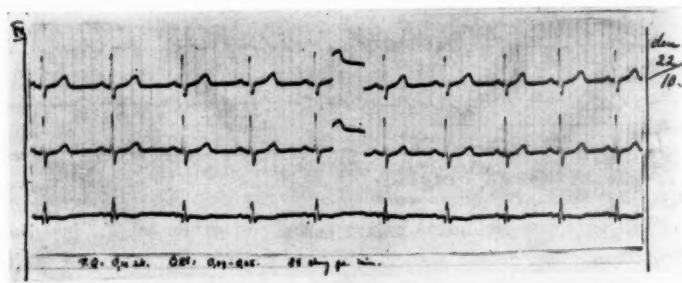


Fig. 4.

but the variation of the P waves is not the one usually found in respiratory arrhythmia with high P waves when the frequency is rapid and low when it is slower. The P waves are very irregular, and in lead III they are negative here and there. The changes indicate intraauricular disturbances of the conductive system. The T waves in this electrocardiogram are more pronouncedly negative than in the foregoing one.

After another day (Fig. 3) the P waves are again normal in lead I and II and diphasic in lead III. In the following electrocardiograms the P waves become more and more clearly positive in lead III, also, and the T waves in the same lead become less markedly negative (e.g. Fig. 4).

According to the Poisonous Drug Act, nicotine is a poison of the first class, and as such may only be sold in retail by the chemist personally, or by some other certified pharmacist; moreover, it may only be sold to well-known and reliable persons, for a specific purpose, e. g. the extermination of vermin. Authorized poison symbols must be affixed to the wrapping in a conspicuous place. On the other hand, patented preparations containing nicotine, e. g. the insecticides 'jofurol' and 'novotoxin' are considered as poisonous substances of the second class, and may be sold in an ordinary shop, but only in well-sealed, unbroken original wrappings. The wrapping must bear the name of the firm of seller and manufacturer, and also the words 'Poison. Beware of use in inhabited rooms'. Thus, the druggist, who had unlawfully supplied a first class poison without even indicating its perils, is the person bearing the prime guilt, but the carelessness of the patient's family makes them partly responsible, also.

Pure nicotine is a very strong poison. About 2—3 drops, corresponding to about 40—60 mg, is considered the lethal dose for an adult.

The insecticides containing nicotine are less poisonous, but far from innocuous. Jofurol, for example, contains 10 % nicotine.

A number of cases from the literature will first be described to illustrate the poisonous nature of nicotine, the swiftness with which it is resorbed, and the different ways in which the poison is introduced into the organism. LOCKHART describes an instance of severe poisoning in a girl employed in the manufacture of a nicotine insecticide. Two drachms (7.5 cc) of a 95 per cent solution of nicotine was spilled on the sleeve of her overalls. She immediately removed the overalls, washed her arm with hot water, wiped off the sleeve, put the overalls on again, and returned to work. Twenty minutes later she collapsed with very grave poisoning symptoms. For half an hour she appeared to be on the verge of death, but finally recovered. FAULKNER communicates a similar case. A 35-year-old man happened to sit down in a chair on the seat of which a little nicotine insecticide (a 40 per cent solution of free nicotine) had been spilled. He felt the solution wet through to the skin over the left buttock, an area

about the size of the palm of his hand, but did not pay much attention to it. After 15 minutes he fell ill with severe poisoning symptoms, and was unconscious for three hours. When he was discharged from hospital four days later, and put on the clothes he had been wearing on admission, he again fell ill with plain signs of poisoning. — JONES and MORRIS describe a case of severe poisoning in a little girl, whose mother had treated her for ringworm by rubbing into the skin a mixture of writing ink and the scrapings from a pipe. McNALLY reviews three cases from the earlier literature: three small children, with death in one and serious illness in the two others, the result of tobacco's being sprinkled on the skin for treatment of favus. Thus, nicotine is quickly and effectively resorbed through the skin; this has also been shown by experiments on animals by FAULKNER, for one. However, peroral poisoning is the commonest. McNALLY also mentioned a case in which an infant aged three years blew soap bubbles with a pipe, and died on the third day. It is not very unusual for children to swallow or chew cigar or cigarette ends, tobacco, snuff, etc. Thus, CRAGG describes how a  $4\frac{1}{2}$ -year-old boy died showing violent symptoms of poisoning 24 hours after consuming snuff. I have myself seen a similar case while I was assistant doctor at the Medical Department of the Eskilstuna hospital. It was a  $1\frac{1}{2}$ -year-old boy who had chewed and swallowed parts of a cigar. Just before this, he had made a hearty meal. He fell ill after a few minutes with violent vomiting and vertigo. On admission to hospital about half an hour later, he was pale, in a cold sweat, and restless, but seemed quite lively otherwise. The heart frequency was rather rapid, but regular. The stomach was rinsed until clear rinsing water was obtained. To begin with, this water smelt plainly of tobacco. A few hours' observation showed the patient to be in apparently good case, and as his parents were absolutely against his staying in hospital, he was allowed to return home. However, the commonest peroral nicotine poisoning is that resulting from the consumption of solutions containing nicotine, when the symptoms often set in with very great rapidity. When pure nicotine has been taken, e.g. with a view to suicide, death may occur either at once or a few minutes

after the poison was taken. ESSER and KÜHN, who collected 44 literature cases, 31 with lethal issue, communicate some cases of instantaneous death after the consumption of the poison, without any symptoms having time to manifest themselves. In a number of others, some minutes elapsed before death. The patient might then have a 'wildly staring gaze' or some short râles as the sole symptoms. Another group, where death did not occur until some hours after the poison had been taken, had a whole series of more or less violent symptoms; these were persons who had taken weaker solutions, pure tobacco, or decoctions of tobacco. As a rule, the rate of the course and the risk of lethal issue seem to increase with the amount of poison taken. There are exceptions, however. Thus, SCHMIDT describes a case where the patient, a 33-year-old man, had attempted suicide by taking 4 cc of pure nicotine; he admittedly became extremely ill at once, but nevertheless recovered. ESSER and KÜHN state that the number of acute nicotine poisonings have been considerably raised by the introduction of nicotine insecticides, and this has been confirmed by others, so that a number of such cases are found in the literature (JOOS, KRATZ, RUDBERG, and others). — There are also cases of nicotine poisoning in the sucklings of hard-smoking mothers. GREINER saw a poisoning of this kind in a 3-week-old infant. The child was perceptibly pale, and had a permanent frown. It was restless and cantankerous, and would neither sleep nor eat; it also had loose faeces, and vomited. It was discovered that the mother smoked 30—40 cigarettes a day, and she was forbidden to do this. The child at once became better, and soon recovered. Several investigators have found and followed up the excretion of nicotine in the breast milk of smokers. EMMANUEL, for example, who also examined the child at the same time, found determinable quantities of nicotine in the breast milk only 1—2 hours after smoking. The excretion reaches its maximum after 4—5 hours. EMMANUEL found toxic symptoms in infants whose mothers smoked 15 cigarettes a day, and he considers that a nursing mother should not smoke more than 6—7 daily. An Italian investigator, MUGGIA, points out that women who smoke too much during pregnancy are more liable to bear premature children than other women.

It was also found that women working in tobacco factories had premature children more often than women in other occupations. A number of pregnant women were investigated while smoking, and a clear increase of the frequency of the foetal heart was found as early as 10—20 minutes after they had finished.

Very serious poisonings may also result from resorption of gases containing nicotine via the respiratory tract, e. g. by tobacco smoking. FRANKE and THOMAS have found no less than 46 cases in the literature where death ensued from nicotine poisoning after tobacco smoking. Others (GENKIN and co-workers, ZILLING and others) describe a number of cases where workers with strong nicotine solutions breathed in the poisonous fumes and were poisoned, sometimes to death.

There are also descriptions of cases where poisoning resulted from nicotine's having been given as an enema for therapeutic purposes. WILLIS narrates how a 5-year-old boy was treated for pinworms by his mother with a water enema, into which she had poured a little strong tobacco decoction. The boy became very ill, but recovered.

The poison may even enter the system by the mucosa of the eye. It is on record that a drop of pure nicotine solution in the eye of a dog is enough to kill the animal.

As LANGLEY and DICKINSON *inter alia* have shown, nicotine has first an irritant and then a paralyzing action on the ganglia cells in the vegetative nervous system. This double action on the vegetative nervous system can therefore elicit remarkably varying symptoms from the different organs of the body. In milder cases of poisoning the gastroenteral symptoms dominate: nausea, vomiting and diarrhoea. The patient also becomes pale, feels dizzy, has muscular quiverings and becomes exhausted. More severe cases are attended by salivation, intense headache, dislike of the light, lowered visual acuity, pin-point pupils, giddiness, uncertain gait, a feeling of oppression over the chest, rapid and difficult breathing, and uneasiness. The worst cases are afflicted with tonico-clonic cramp, which passes into general paralysis, arrested breathing, and death. In addition, the more severe cases show more pronounced cardiovascular symptoms such as pallor,



cold extremities, subnormal temperature, cold sweats, cyanosis, and almost always bradycardia with a pulse frequency down to 35—40 beats a minute (SCHMIDT, GENKIN and co-workers, FRETWURST, GOTSEV and HERTZ, etc.) and a thready pulse. The blood pressure is low. There is sometimes tachycardia also (SSALISCHTSCHEFF and TSCHERNOGOROFF, JOOS, and others), extrasystoles of varying type, and sinus arrhythmia. Negative T waves in one or more leads and P waves varying in form and shape, like those of the case described in this essay, have previously been registered by FRETWURST and HERZ, GENKIN and co-workers, and others. However, the literature contains remarkably few cases that were followed with electrocardiograms, and I have not been able to find any case that combined such marked electrocardiogram changes with such slight symptoms otherwise. These electrocardiogram changes have been interpreted by FRETWURST and HERZ, SSALISCHTSCHEFF and TSCHERNOGOROFF, and others, as due to the action of the nicotine on the vegetative nervous system, particularly the vagus, and not as real myocardiac lesions. Indeed, the changes usually subside very rapidly on the return of health. It is also interesting that the blood sugar is raised under the influence of nicotine (BURSTEIN and GOLDENBERG, LUNDBERG, and others), and there is not infrequently glycosuria. This rise of the blood sugar curve is attributed to an increased outflow of adrenaline due to the poisoning.

The autopsy of cases of nicotine poisoning does not offer anything of special interest. No findings characteristic of nicotine poisoning are revealed, either macroscopically or microscopically. However, using a special technique in experiments on microscopic sections from the removed heart of dogs, MOCHIZUKI has shown changes in the ganglia cells due to nicotine.

The treatment of the acute nicotine poisonings is a not very encouraging subject, in view of the rapidity with which nicotine is resorbed and the lack of a therapeutic medium which would neutralize its effect. Rinsing out the stomach is not much use in the peroral poisonings, if the patient cannot be treated immediately after the consumption of the poison; nevertheless, this measure should be taken, particularly if there is reason to



suppose that the patient has got tobacco products into his organism. FRANKE and THOMAS, who experimented with dogs, very strongly recommend artificial respiration started before the circulation has failed and continued until muscular paralysis passes off. They interpret the respiratory paralysis as a paralysis of the peripheral neuromuscular mechanism, and have not found any central action, either on the respiratory or on the vasomotoric system. For the rest, the literature prescribes the customary vascular stimulants (coramine etc.) in large doses, combating of the subnormal temperature with hot-water bottles in the bed, wrapping in blankets, and hot baths, and the attacks of cramp with sedatives.

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**Poliomyelitis and its Prognosis in Sweden.**  
**Condition and Capacity for Work after Nine Years' Observation.**

By

**ROLF BERGMAN.**

1. During the years 1942—1944 the author surveyed 454 patients, who during the years 1934—1936 had been nursed as cases of acute poliomyelitis in the Stockholm Hospital for Communicable Diseases. 313 (192 men, 121 women) were cases of paresis, 141 (80 men, 61 women) had displayed all the symptoms typical of poliomyelitis except for paresis, »abortive cases». The 85 per cent of the cases (260 of which were cases of paresis) that fell ill in the city of Stockholm represent the town's morbidity in poliomyelitis quite well.

Of the 454 cases 72 were dead in 1942; 62 of poliomyelitis. Of the survivors 233 cases (94 per cent) and 110 abortive cases (81 per cent) were available for control examination. A few of these could, however, not be subjected to all the examinations reported below.

In 25 per cent of the 313 cases of paresis some cranial nerve was affected, in 11 per cent that was the only lesion; 31 per cent had isolated pareses of the trunk, arms or legs, 23 per cent displayed pareses of the muscles of the legs as well as of the arms and trunk, the remainder suffered from less extensive combined pareses. The patients in the age-group 0—14 years suffered from limited pareses more frequently than did the older ones. On the other hand there was no difference between men and women.

2. *Epidemiologically* the examination of the 260 cases of paresis that had fallen ill in Stockholm disclosed the following facts:

The age distribution will be seen from the Diagram.

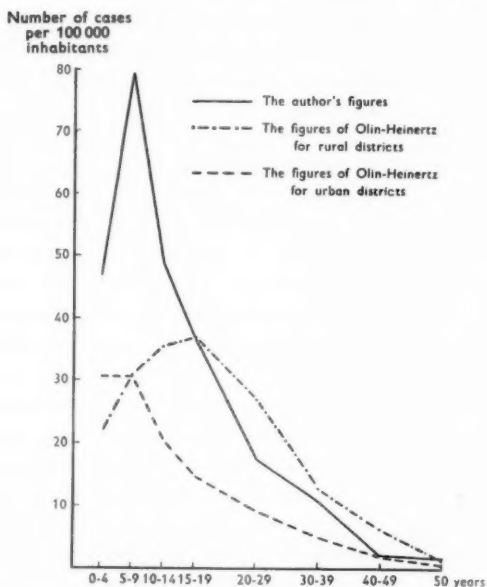


Diagram showing the age-distribution in the author's material and in that of OLIN-HEINERTZ.

In the diagram a comparison is also made between the author's figures and those obtained by OLIN and HEINERTZ (1) for the whole of Sweden for the years 1930—1939. Except for the first 5-year group the agreement is good. The youngest patient was 1 month old, the oldest 58 years old. Men and women had an average morbidity of 0.08 ‰, women 0.33 ‰.

A certain agglomeration of the cases is discernible. The areas in Stockholm that had the highest frequency are the same as those found by the author to have the highest scarlatina and diphtheria morbidity respectively. The children (0—14 years) are represented a little more strongly there than in other areas. There cannot be discerned any connection between the frequency and the distribution of drinking-water.

The seasonal distribution of paresis is that typical in Sweden; the maximum of the distribution curve is in September—October

but varies somewhat from year to year without there being any connection with the mean air temperature measured in Stockholm.

3. The case fatality ratio (cases of paresis in Stockholm) was 15.8 per cent; for men 20.5 per cent, for women 8.1 per cent with statistically significant difference. The case fatality ratio was definitely lower before than after 10 years of age. It seems to be highest in the age-group 15—19 years (not statistically proved) and for women it decreases manifestly after the age of 20. The case fatality ratio is lowest in the cases of isolated pareses in the legs, arms and trunk (0 per cent) and highest when the whole skeletal muscle is affected (40 per cent); the cases suffering from paresis of the cranial nerve displayed a case fatality ratio of 26 per cent.

The mortality is highest in the age of adolescence (15—19 years). It is especially high in the age-group 10—14 years. This is due to the fact that the case fatality ratio as well as the morbidity is high in these age-groups. In the ages 0—9 years and most especially in the age-group 0—6 years the number of deaths is smaller, comparatively, which will be especially due to the lower case fatality ratio for that age-group. The lower mortality after the age of 20 will, on the other hand, be due to the limited spread of the disease.

In cases suffering from respiratory paresis the case fatality rate was 73 per cent. Now that we are able by the aid of the respirator to save many cases suffering from paresis of the respiratory muscles, it is generally a bulbar paralysis with a circulatory insufficiency that is the cause of death. It is apparent, however, that the cases suffering from a partial or relative paralysis of the respiratory muscles have also very little resistance against secondary infections.

4. *The orthopedic prognosis*, as it appears in the control examination, after about 9 years, of a material comprising patients that were taken ill in as well as outside Stockholm, seems to be comparatively good (313 cases).

60.5 per cent of the cases of paresis that did not succumb to their acute poliomyelitis and that did not die of a complication, were when controlled practically restored as regards the function

of the muscles. — 35.2 per cent had no symptoms of paralysis. 19.3 per cent had remaining slight pareses, 12.4 per cent had moderate, 6.9 per cent had severe, and 0.9 per cent had very severe ones. These figures agree very well with those obtained by other Swedish investigators.

The women displayed remaining moderate or severe pareses more frequently than did the men (29.9 and 13.2 per cent resp.). In the group comprising those with the most favourable prognosis — those completely restored — we find 41.9 per cent of the men examined but only 25.8 per cent of the women.

Although there is no reliable statistical support for the statement, the investigation would nevertheless appear to indicate that the most favourable results from an orthopedic point of view are commonest among the cases that were afflicted before the age of 15 and that the group comprising 15—19 year-olds has the poorest invalidity prognosis.

The prospects of avoiding pronounced crippling and of regaining a comparatively satisfactory functioning of the muscles are greater in the cases suffering from the least extensive pareses. Practically all the survivors with paresis only of the cranial nerves — cf. p. 4 — recover completely.

A comparison between the orthopedic condition of the patient at the end of the acute stage, when he left the hospital after about 3—4 weeks' nursing, and his condition when controlled about 9 years later, disclosed that 38 per cent of the cases examined reached their final orthopedic state very rapidly. Children and adults, men and women, appeared alike in this respect. 9 per cent of the 233 cases controlled had recovered completely from their paresis during their stay in hospital.

In 10 per cent of the cases the control examination showed that a weakness of the muscles existed in patients who had been considered to be without paresis while in hospital and when leaving the hospital.

5. *Prognosis as regards capacity for work.* The capacity for work is naturally dependent upon the patient's orthopedic condition. However, the ability of the patient to get on in spite of the functioning of his muscles being defective also depends on

his age, intelligence, energy, previous activity, possibilities of training and re-schooling, financial resources, etc. An examination of the patient's orthopedic condition and of the capacity for work as demonstrated by him will therefore in some cases disclose a palpable discrepancy.

An examination of the patient's capacity for work about 9 years after the attack of poliomyelitis could be carried out in 215 cases. It disclosed that 78 per cent of those controlled could get along financially and socially by their own work (51 per cent having complete capacity for work, 27 per cent good capacity). 17 per cent were partly capable of doing work, for instance in special trades, and only 5 per cent were incapacitated for work. These figures give a different picture of the risk of crippling to that obtained solely by the orthopedic examination. When making a prognosis it is consequently always necessary to consider the medical as well as the social examinations.

The author's figures display good agreement with those recently found by two other Swedish investigators.

Observation period . . . . .	BERGMAN (215 cases) abt 9 years 1945	NETTELBLAD (2) (121 cases) abt 2 years 1939	JÖNSSON (3) (210 cases) abt 6 years 1944
Complete capacity for work (all trades) . . . . .	54 %	44.6 %	—
Good capacity . . . . .	78 %	76.0 %	72 %
Partial capacity . . . . .	17 %	17.4 %	25 %
Incapacity for work . . . . .	5 %	6.6 %	3 %

No differences in the prognosis, as regards the capacity for work, could be established between the various age-groups. A greater percentage of men than of women displayed complete or good capacity for work, which agrees well with the orthopedic findings (p. 301).

The extensive pareses (leg + arm + trunk paresis) had the poorest prognosis as regards capacity for work. Only 42 per cent reached complete capacity, while 82 per cent of the cases suffering from leg- or arm- or trunk-paresis only regained complete capacity.

6. *Respiratory paresis.* Out of the 30 cases which in view of their very poor condition were treated in the Sahlin respirator, only 5 (13 per cent) survived. 4 cases treated in the Thunberg barospirator died. The survivors after respiratory paresis of course frequently suffer from severe remaining pareses, though in the present material only 3 of the 16 survivors were completely incapacitated for work. 3 reported good, 1 complete capacity for work. Respiratory paresis is thus not an absolutely hopeless complication, and not even when it during the acute stage appears to threaten the life of the patient, should one despair of saving his life or of regaining for him a fitting life in society.

7. *The prognosis for the abortive cases* has earlier been considered definitely good. Although the present investigation was not really intended to go into that question, the results obtained would seem to indicate that we should be more reserved on this point. In 35 per cent of the abortive cases the control examination disclosed that the patient suffered from a more or less serious and palpable nervous or psychical morbid condition considered to be attributable to his poliomyelitis.

8. *Poliomyelitis as an endemic disease in Sweden.* In Sweden, with somewhat more than 6 million inhabitants, we have an average of 8—900 cases of poliomyelitis annually. Of the survivors, about 700 cases, approximately 150 may be anticipated to require financial support for the rest of their lives and many of these cases should be taken care of by the community in nursing-homes of various kinds.

This annual increase in the number of more or less crippled persons is certainly quite a burden for the community, but what is more important is that many of them do not until after several years of frequently intensive treatment reach the good orthopedic condition here recorded and thus a satisfactory capacity for work. Only 10 per cent were entirely free from paresis when they left the hospital; many of them — in this investigation 49 per cent — had to be admitted into orthopedic hospitals immediately after leaving the hospital for communicable diseases and many others had to be given orthopedic treatment as out-patients, in this material 13 per cent. As conditions in Stockholm are especially



favourable for polyclinic treatment or nursing in the home, it would appear reasonable to calculate that for the country as a whole considerably more than half the number, i. e. 3—400 cases a year, must be afforded places as patients in the orthopedic departments. As this treatment must frequently be for quite a considerable period of time, this is a great nursing problem.

### Conclusions.

Poliomyelitis is a serious endemic disease in Sweden, costing many lives in our best age-groups and producing a not inconsiderable invalidity. Judging from the present investigation, the result of which is supported by two other Swedish investigations, it would appear, however, that we have earlier overrated the risk of crippling. In many cases we may hope that the patients may escape complete invalidity or a serious restriction of their capacity for work. A condition precedent for the realization of these hopes is, however, that we can give our poliomyelitis patients good care in the acute stage as well as during the long period of after-treatment.

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AUS DER PÄDIATRISCHEN KLINIK DES KAROLINISCHEN INSTITUTES IM  
KRANKENHAUS NORETULL (VORSTAND: PROF. A. WALLGREN) UND DER  
ABTEILUNG FÜR ALLGEMEINE PATHOLOGIE DES KAROLINISCHEN IN-  
STITUTES IM KRANKENHAUS SABBATSBERG (VORSTAND:  
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## **Die Skelettentwicklung bei infantiler Hyperthyreose.**

### **Eine experimentelle Untersuchung.**

Von

**CARL GUSTAF BERGSTRAND.**

Bei den Erkrankungen der Drüsen mit innerer Sekretion spielen Veränderungen im Bereich des Knochengerüsts oft eine bedeutsame Rolle. Ganz besonders wichtig ist aber die Untersuchung des Skelettsystems dann, wenn endokrine Störungen das heranwachsende Individuum betreffen.

Bei der infantilen Hypothyreose, deren klinisches Bild bekanntlich von geistigem und körperlichem Zurückgebliebensein beherrscht wird, ist das röntgenologische Studium des Skeletts in hohem Grade wegweisend für die Diagnose und in gewissem Umfang auch für die Therapie (SHELTON 1933). Wie wir wissen, findet man im Handskelett, welches das gewöhnlichste Untersuchungsobjekt sein dürfte, eine erhebliche Entwicklungsverzögerung der Knochenkerne, die in gewissen Fällen mehrere Jahre betragen kann.

Als ein Gegenstück hierzu kann man bei unbehandelten Fällen, die über die Pubertätsjahre hinausgekommen sind, feststellen, dass der Epiphysenknorpel überhaupt nicht verknöchert oder der Sitz einer unvollständigen und unregelmässigen Verknöcherung ist.

Die Skelettveränderungen beim endemischen Kretinismus sind im Prinzip dieselben wie bei der angeborenen kindlichen Hypothyreose (LOOSER 1929).

Die Veränderungen beschränken sich indessen nicht nur auf eine mangelnde Reifung des Knorpels, sondern es ist auch der

Wachstumsprozess aufgehalten; dies hat eine Verkürzung der langen Röhrenknochen zur Folge, eine Veränderung, die sich bei Exstirpationsversuchen an Tieren sehr schön reproduzieren lässt (DOTT 1923, HAMMET 1929 u. a.).

Bei der Hyperthyreose junger Individuen sind die Verhältnisse wesentlich komplizierter, was aus sowohl klinischen Beobachtungen wie tierexperimentellen Untersuchungen hervorgeht. Was da zunächst das Wachstum anlangt, so ist dieses ein äusserst verwickelter Vorgang, bei dem unter den endokrinen Faktoren die Schilddrüsenfunktion eine freilich wichtige, doch bei weitem nicht die allein ausschlaggebende Rolle spielt. Im Hinblick auf die Hemmung des Wachstums bei mangelhafter Schilddrüsentätigkeit könnte man vielleicht erwarten, dass junge Personen mit Hyperthyreose ein gesteigertes Längenwachstum und infolgedessen eine für ihr Alter übermässige Körpergrösse aufweisen würden. Diese Ansicht ist auch die im Schrifttum am häufigsten vertretene (ŠEREŠEVSKIJ 1931, BRAM 1937, REILLY 1940, KENNEDY 1940, LERMAN 1941, HERTZ und GALLI-MAININI 1941, SIEGL 1942).

TOPPER (1931) studierte das Längenwachstum bei 16 körperlich und geistig zurückgebliebenen, nicht hypothyreotischen Kindern, welche Schilddrüsenpräparate erhielten. Zwölf von diesen Kindern hatten normale Grundumsatzwerte und reagierten auf die Zufuhr von Schilddrüsensubstanz mit einer Zunahme der Körpergrösse, die über die Norm hinausging, ohne irgendwelche hyperthyreotischen Symptome erkennen zu lassen. Ein derartiges Experiment in grossem Massstab an völlig normalen Kindern würde ausserordentliches Interesse besitzen, ist aber, soweit es Verf. bekannt ist, bisher nicht vorgenommen worden und lässt sich wohl auch aus zahlreichen Gründen nicht durchführen.

Die Hyperthyreose im Kindesalter ist, wenigstens in europäischen Ländern, ein verhältnismässig seltener Zustand, und die Diagnose ist in vielen Fällen schwierig. Symptome wie Tachykardie und Nervosität sind schwerer zu beurteilen als bei Erwachsenen; ferner bereitet die Bestimmung des relativen Umsatzes, zumindest bei jüngeren Kindern, gewisse Schwierigkeiten, und muss mit Kritik bewertet werden.

SATTLER gibt in Graefe-Saemischs Handbuch der gesamten

Augenheilkunde 1910 an, dass von 3488 Fällen der Basedowschen Krankheit 184 jünger waren als 15 Jahre. Dieses ältere Schrifttum, dass man zum Teil nicht mehr im Original lesen kann, enthält viele Fälle, wo die Diagnose bei heutiger Betrachtungsweise in hohem Grade unsicher ist. Es fehlt auch die Kontrolle, welche das klinische Laboratorium jetzt in Form von Bestimmung des relativen Umsatzes, des Blutcholesterins usw. geben kann. Akzeptiert man indessen die in der Sattlerschen Arbeit angeführten Fälle als hyperthyreotische Zustände im Kindesalter, so findet man, dass das Material keine eindeutigen Angaben liefert und kaum als ganz sicherer Beleg für die Annahme gelten kann, dass die Hyperthyreose zu einer Steigerung des Längenwachstums führt.

Die einzige systematische Untersuchung über einschlägige Fragen, die Verf. im älteren Schrifttum finden konnte, ist I. HOLMGRENS Arbeit vom Jahre 1909. Das bemerkenswert grosse Material besteht zum überwiegenden Teil aus Mädchen im Pubertätsalter und etwas älteren; es ergibt sich für die jüngeren Individuen eine Zunahme der Körpergrösse bei denjenigen Fällen, die Holmgren als Morbus Basedow oder mit diesem Leiden verwandte Zustände auffasst. Der Autor, dessen Untersuchung ausgeführt worden war, bevor die Laboratoriumstechnik ihren heutigen Stand erreicht hatte, stützt sich bei seiner Diagnose hauptsächlich auf die Trias Struma, Tachykardie und Tremor. In Unkenntnis des Verhaltens des relativen Umsatzes bei diesen Fällen dürfte es sicherer sein, das besagte Material nicht als ganz vollgültigen Beweis dafür zu betrachten, dass die Hyperthyreose in den Kinder- und Jugendjahren ein gesteigertes Längenwachstum bewirkt. Die Schwierigkeiten, Fälle von dem Typus zu beurteilen, wie sie Holmgren beschrieben hat, wird auch im Schrifttum betont (KLEIN 1922, NOBEL und KORNFELD 1936).

In der neueren Literatur, in der die Diagnose in vielen Fällen gesichert sein dürfte, fehlen bedauerlicherweise oft Angaben über Gewicht und Körpergrösse, und es scheinen nur wenige grössere Zusammenstellungen vorzuliegen, deren Gegenstand die Körperlänge bei juvenilen Hyperthyreosen ist. GRAM (1922) beschreibt

3 Fälle von juveniler Hyperthyreose und gibt für alle an, dass die Länge grösser war als normal. Beachtenswert ist, dass bei einem Fall, wo der Kropf im Alter von 14 Jahren operiert worden war, nach der Operation das Längenwachstum aufhörte, ohne dass sich irgendwelche Anzeichen von Hypothyreose feststellen liessen (histologisch bot die Struma das Bild einer Kolloidstruma dar; Angaben über präoperative Jodbehandlung enthält die betreffende Arbeit nicht). GRAM äussert den Gedanken, dass die Entwicklung unter dem Einfluss der Hyperthyreose rascher vonstatten geht und eher als normal zum Abschluss kommt. HEIMAN (1923), NOBEL (1932), BILMANN (1935), WALLIS (1935) und PETERSÉN (1941) berichten über — insgesamt 8 — Fälle, welche eine mehr oder minder markante Steigerung der Körpergrösse gegenüber der Norm erkennen liessen. Von amerikanischer Seite sind reichhaltigere Fallsammlungen veröffentlicht worden (in gewissen Arbeiten über hundert Fälle), und Untersuchungen von REILLY (1940), KENNEDY (1940) sowie HERTZ und GALLI-MAININI (1941) weisen im grossen und ganzen übereinstimmende Ergebnisse auf. Diese Autoren stehen auf dem Standpunkt, hyperthyreotische Personen bis zu einem Alter von 18—20 Jahre seien hochwüchsiger als normal, während bei älteren Individuen keine sichere Abweichung im Vergleich zu Gleichaltrigen zu konstatieren sei. HERTZ und GALLI-MAININI, die ihr Material längere Zeit beobachtet hatten, konnten das vermehrte Längenwachstum während der Krankheit deutlich demonstrieren, machten aber auch die interessante Feststellung, dass die Wachstumssteigerung in vielen Fällen länger zurücklag als das klinische Manifestwerden des Leidens. Auch REILLY gelangte zu ähnlichen Schlussfolgerungen.

Betrachtet man die Arbeit von KENNEDY genauer, so findet man auf der anderen Seite, dass bei einem nicht unwesentlichen Teil der Fälle des Autors die Körpergrösse unter der Norm lag. KLEIN (1922) gibt ebenfalls an, dass von drei Fällen von juveniler Hyperthyreose zwei in der körperlichen Entwicklung zurückgeblieben waren. BLOOM (1935) »with 26 cases under 14 years of age noted growth as distinct from body weight and stated that there was a 'general retardation'» (zit. n. SMITH und McLEAN

1938). CRILE und BLANTON haben 1937 einen Fall von Hyperthyreose bei einem 2 $\frac{1}{2}$ jährigen Knaben beschrieben. Der Längenzuwachs betrug während einer Zeit von 8 Monaten 7 cm, was kaum als abnorm gelten kann. Auch über Fälle mit normaler Körpergrösse ist im Schrifttum berichtet worden.

Es erscheint somit schwer, aus den in der Literatur zugänglichen Angaben ganz sichere Schlussfolgerungen darüber zu ziehen, wie sich der Grössenzuwachs bei Individuen mit Hyperthyreose während der Jahre des Heranwachsens verhält.

Wendet man sich tierexperimentellen Untersuchungen über das Wachstum bei Verabreichung von Schilddrüsensubstanz zu, so findet man auch hier Ergebnisse, die in geradem Gegensatz zueinander stehen.

MOUSSU (1899) und SCHAFER (1912) waren der Ansicht, die Schilddrüsenzufuhr steigere bei jungen Tieren das Wachstum, während BIRCHER (1910) zu dem entgegengesetzten Resultat kam, und zwar in bezug auf sowohl Gewicht wie Länge der Röhrenknochen und das allgemeine Aussehen der Tiere. HERRING (1917) zeigte, dass junge Ratten, die Schilddrüsensubstanz erhielten, keine sichere Veränderung bezüglich der Körperlänge erkennen liessen, aber eine Abnahme des Körpergewichts im Vergleich zu dem der Kontrolltiere, was mit den Ergebnissen, zu welchen E. R. HOSKINS (1916) gelangt war, im Einklang steht. CAMERON und CARMICHAEL (1920) meinten, bei den Versuchstieren sei das Wachstum geringer. DOTT (1923) beobachtete bei jungen Hunden eine Längenzunahme der langen Röhrenknochen, aber auf diese folgte ein verfrühter Stillstand des Wachstums: »Growth is accelerated, but maturity is disproportionately hastened, so that the stature becomes fixed at a subnormal limit by epiphyseal ossification.« DURRANT (1928) glaubte, seine Versuchstiere (Meerschweinchen) wüchsen weniger rasch als die Kontrolltiere aus demselben Wurf. SMITH und McLEAN (1938) meinten nachweisen zu können, dass das Wachstum der langen Röhrenknochen bei der Ratte während der Zufuhr maximaler Dosen von Schilddrüsensubstanz geringer wurde.

Eine mangelhafte Schilddrüsenfunktion bei jungen Individuen hat, wie bereits erwähnt, eine Verminderung oder Aufhebung des

Längenwachstums und eine Störung des Reifungsprozesses zur Folge. Aus den klassischen Versuchen von GUDERNATSCH an Kaulquappen wird in schöner Weise ersichtlich, dass sich andererseits, was den Vorgang der Reifung und Differenzierung anlangt, dieser durch Zufuhr von Schilddrüsenpräparaten beschleunigen lässt. Dass dies auch für Säugetiere gilt, erhellt aus manchen Tierversuchen.

Wenn es sich um menschliches Material handelt, sind, soweit Verf. finden konnte, die Beobachtungen recht dünn gesät. TOPPER (1931), der oben zitiert worden war, glaubte bei seinem Material von körperlich zurückgebliebenen, nicht hypothyreotischen Kindern, die Schilddrüsenpräparate erhalten hatten, mindestens in zwei Fällen Anlass zu dem Verdacht zu haben, dass Zahnen und Skelettentwicklung schneller vonstatten gingen. Eine von mehreren Autoren gemachte Feststellung ist die, dass sich die Knochenkerne bei hypothyreotischen Individuen unter dem Einfluss der Schilddrüsendarreichung nicht nur bis zur Norm für das Alter, sondern auch weit über diese hinaus entwickeln (WILKINS 1938, MANNHEIMER 1937). Das »Knochenalter« kann in gewissen Fällen das Lebensalter um mehrere Jahre übersteigen. MUSSIO-FOURNIER und CERVINO (1932) haben einen Fall von Mongolismus beschrieben, der bei Thyreoideamedikation eine abnorm rasche Knochenkernentwicklung aufwies.

Bei Hyperthyreose jugendlicher Individuen wäre infolgedessen eine abnorm vorgeschrittene Entwicklung von Knochenkernen zu erwarten. Diesbezügliche Beobachtungen sind indessen spärlich. Nach RIBBING (1941) waren die Handknochen bei einem 10jährigen Kinde mit Basedow völlig normal. Bei dem oben angeführten, von CRILE und BLANTON (1937) beschriebenen Falle von Basedowscher Krankheit bei einem 2  $\frac{1}{2}$  jährigen Knaben entsprach dagegen die Skelettentwicklung der eines 5jährigen. Ähnliche Feststellungen sind von BILMANN (1935), WALLIS (1935), REILLY (1940) und PETERSÉN (1941) gemacht worden. HOLMGREN hat ebenfalls in seinem Material die Entwicklung des Knochengerüsts studiert und eine vorgeschrittene Verknöcherung gefunden, die er allerdings bei grossen heranwachsenden Individuen ganz allgemein konstatieren zu können glaubte.

M. M. HOSKINS (1927) injizierte neugeborenen Ratten Azetylthyroxin und konnte zeigen, dass sich der Schädel bei diesen Tieren binnen verhältnismässig kurzer Zeit veränderte und die für das ausgewachsene Tier charakteristische Form annahm. Bei den Kontrolltieren verlief die Entwicklung deutlich langsamer. HOSKINS beobachtete ferner, dass sich bei denjenigen Tieren, welche Azetylthyroxin erhielten, die Epiphysen eher entwickelten; leider aber sind die der Arbeit beigelegten Röntgenbilder des Extremitätenskeletts der Ratten unbefriedigend und entziehen sich jeglicher Beurteilung. Auch das Zahnen war bei den Versuchstieren beschleunigt, eine Feststellung, welche KARNOFSKY und CRONKITE (1939) bestätigt haben. Neben den interessanten Veränderungen am Knochengerüst konstatierte HOSKINS noch ein rascheres Fortschreiten der allgemeinen Entwicklung der Versuchstiere, obgleich diese kleiner waren als die Kontrolltiere. Bemerkenswert ist, dass das von HOSKINS verwendete Präparat Azetylthyroxin laut ihrer eigenen Angaben bei ausgewachsenen Säugetieren keinerlei Einfluss auf den Stoffwechsel ausübt.

Auch über das histologische Aussehen des Epiphysenknorpels beim experimentellen Hyperthyreoidismus liegen etliche Untersuchungen vor. BIRCHER (1910) konnte bei jungen Ratten, die 4 Monate lang Thyreoideatabletten erhielten, nachweisen, dass die Epiphysenlinien im Röntgenbilde ganz oder so gut wie ganz fehlten und histologisch nur aus einer schmalen Knorpelzone bestanden. Bei DORRIS (1923) Versuchen an jungen Hunden, allem Anschein nach mit verhältnismässig langdauernder Zufuhr von Thyreoideapräparaten, wurde der Epiphysenknorpel ebenfalls schmaler als normal und wies histologisch Anzeichen einer rascheren Differenzierung und vorzeitigen Verknöcherung auf. STEFANESCU (1926) kam bei Versuchen an Meerschweinchen zu demselben Ergebnis bezüglich der Breite des Epiphysenknorpels und bemerkte eine Unregelmässigkeit in den Zellen der Pfeilerzone sowie eine gesteigerte Verbreitung der verkalkten Knorpelzellen. CORYN (1936 und 1939) injizierte einem 1 Monat alten Kaninchen kleine Dosen Thyroxin und fand nach dreissig Tagen, dass sich im Epiphysenknorpel Zonen blasigen Knorpels (*«cartilage hypertrophique»*) auf Kosten der Pfeilerzone (*«cartilage sérié»*) aus-



gebreitet hatten. »L'hyperthyroïdie accélère la prolifération et rend l'hypertrophie plus précoce.» SMITH und McLEAN (1938) untersuchten gewisse Veränderungen am Skelett bei Ratten, denen im Laufe mehrerer Monate maximale Schilddrüsendosen zugeführt wurden, und konstatierten, dass der Epiphysenknorpel histologisch ein Bild darbot, das auf ein Aufhören des Wachstums hindeutete. Die Abbildungen zu der Arbeit machen ersichtlich, dass der Epiphysenknorpel schmaler ist als normal, und dass die Zone des blasigen Knorpels praktisch verschwunden ist. M. und R. SILBERBERG (1938), die sich mit dem Einfluss verschiedener Hormone auf das Skelett, namentlich auf den Epiphysenknorpel, eingehend beschäftigt hatten, glauben indessen nachgewiesen zu haben, dass letzterer bei Meerschweinchenjungen nach Behandlung mit Schilddrüsen-tabletten nicht nur eine raschere Differenzierung erfährt, sondern auch ein schnelleres Wachstum als in der Norm aufweist. Histologisch kommt dies in einer Verbreiterung des Epiphysenknorpels mit einer zahlenmässigen Zunahme der Zellen zum Ausdruck, wobei die Zellvermehrung im Bereich des blasigen Knorpels vorherrscht. In einer zusammenfassenden Darstellung (1941) geben die Autoren an, dass das Schilddrüsenhormon, ebenso wie Vorderlappenextrakt und Jodkali, ein verfrühtes Altern des Skeletts mit Beschleunigung sowohl der Proliferations- wie der Differenzierungsprozesse im Knorpel verursacht.

Unter verschiedenen Versuchsbedingungen müsste man also diese Vorgänge in verschiedenen Entwicklungsphasen erfassen können, und hierdurch würde sich vielleicht eine Erklärung dafür ergeben, dass der Epiphysenknorpel unter dem Einfluss des Schilddrüsenhormons sowohl breiter wie auch schmaler werden kann, als es normalerweise der Fall ist.

#### *Eigene Untersuchungen.*

Von der klinischen Erfahrung ausgehend, dass sich die Knochenkerne bei der kindlichen Hypothyreose unter dem Einfluss der Substitutionstherapie mitunter rascher entwickeln können als normal, und dass die Verknöcherung bei hyperthyreotischen Zuständen im Wachstumsalter abnorm weit vor-

geschritten sein kann, hat Verf. eine tierexperimentelle Untersuchung angestellt, um die Entwicklung der Knochenkerne bei Zufuhr von Schilddrüsenpräparaten zu studieren.



Abb. 1. Röntgenbild des linken Hinterbeins.  
Sechs Tage altes Kaninchen.

Als Versuchstier wurde aus mehreren Gründen das Kaninchen gewählt. Beim neugeborenen Kaninchen ist das Knochengerüst unvollständig entwickelt. In den hinteren Extremitäten sind bei der Geburt u. a. die proximale und distale Fibulaepiphyse sowie die distale Tibiaepiphyse nur als Knorpel angelegt. Im Tarsus sind lediglich Calcaneus und Talus verknöchert. Das Skelett erfährt dann eine bemerkenswert rasche Entwicklung, so dass nach einigen Wochen sämtliche Knochenkerne in den hinteren Extremitäten voll ausgebildet sind.

Verf.s Material besteht aus 10 Versuchs- und 9 Kontrolltieren, die aus 4 Würfen stammen. Das Verhältnis zwischen Versuchstieren und Kontrollen ist in den einzelnen Würfen folgendes: 2 : 1, 3 : 2, 2 : 3 und 3 : 3. Die Versuche wurden damit eingeleitet, dass die Kaninchenjungen einige — höchstens 6 — Tage nach der Geburt gewogen wurden, worauf ein Röntgenbild des linken Hinterbeins aufgenommen wurde. Dieses zeigt bei sämtlichen Tieren dieselbe Entwicklung des Skeletts; das Aussehen wird aus Abb. 1 ersichtlich. Die Geburtsgewichte schwankten innerhalb der einzelnen Würfe nur unerheblich, und die Kontrolltiere wur-

den, sofern dies möglich war, so gewählt, dass ihr Gewicht sowohl nach oben wie nach unten entsprechend demjenigen der Versuchstiere wechselte.

Es ist mit recht grossen Schwierigkeiten verknüpft, bei so jungen Tieren wie denjenigen, um welche es sich hier handelt, und die während der ganzen Versuchszeit von den Muttertieren gesäugt wurden, Schilddrüsenpräparate per os zuzuführen; Verf. hat infolgedessen injizierbare Präparate verwendet.

Vier Tiere erhielten Thyroxin (Roche) und sechs Thyranon, einen von Pharmacia AG. hergestellten gereinigten Schilddrüsenextrakt, von dem 1 ml ungefähr 0,06 mg Thyroxin entspricht. Die zugeführten Dosen schwankten etwas bei den einzelnen Würfen, aber im grossen und ganzen wurde nach folgendem Schema vorgegangen: Die Tiere bekamen (nach dem Wiegen und Röntgenphotographieren) an den beiden ersten Tagen  $\frac{1}{2}$  ml Thyroxin bzw. 2 ml Thyranon und dann im allgemeinen jeden zweiten Tag 1 ml Thyroxin bzw. 4 ml Thyranon. Insgesamt wurde den Tieren mindestens 4 ml Thyroxin bzw. 16 ml Thyranon, höchstens 7 ml von jenem bzw. 28 ml von diesem Mittel zugeführt. Bei denjenigen Würfen, wo die Gesamtmenge kleiner war, ergab sich dasselbe Resultat wie bei denen mit grösserer Gesamtdosis. Versuche, kleinere Einzeldosen von Thyranon (2 ml) zu injizieren, führten nicht zu sicheren Ergebnissen. Kleinere Einzeldosen Thyroxin wurden nicht versucht. Die Injektionen erfolgten in sämtlichen Fällen subkutan.

Die verwendeten Dosen sind bemerkenswert gross. Mit zweimal wöchentlich  $\frac{1}{2}$ —2 ml Thyranon lässt sich laut Angaben bei erwachsenen Menschen ein befriedigender Thyreoideaeffekt erzielen. Es hat demnach den Anschein, als ob neugeborene Kaninchenjunge eine beträchtliche Widerstandsfähigkeit gegen die angewendeten Präparate besässen; auf der anderen Seite aber gingen mehrere Versuchstiere vor Abschluss des Versuchs ein, und es gelang auch nicht, die Kaninchen eine einigermassen längere Zeit am Leben zu erhalten, wenn diese grossen Dosen gegeben wurden. Kleinere Mengen, die in einigen Fällen (im Material nicht enthalten) versucht wurden, beeinträchtigten das Befinden der Tiere selbst dann nicht, wenn sie

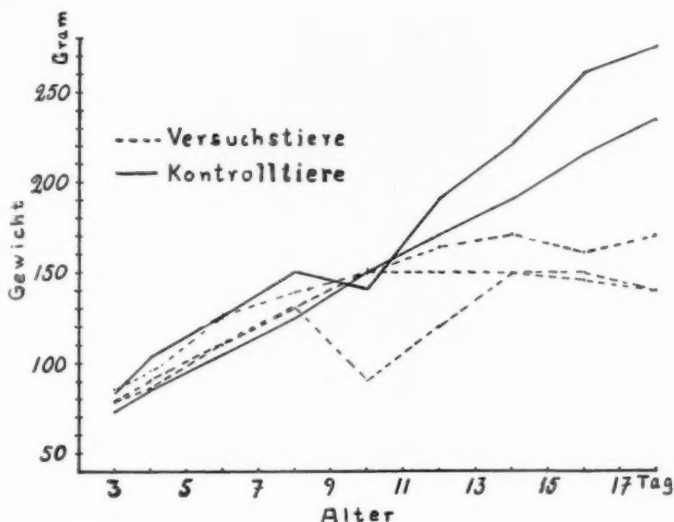


Abb. 2.

längere Zeit zugeführt wurden, und übten auch keinen sicheren Einfluss auf die Verknöcherung aus.

Die Tiere wurden jeden zweiten Tag gewogen, und die Versuchstiere nahmen anfangs gleichlaufend mit den Kontrolltieren zu, um dann nach etwa einer Woche eine langsamer steigende, stillstehende oder sinkende Gewichtskurve aufzuweisen. Diese Abweichung bezüglich des Gewichts trat ein, als die Versuchstiere 12—16 ml Thyranon bzw. 3—4 ml Thyroxin erhalten hatten. Die Gewichtskurven für die einzelnen Würfe verhalten sich im grossen und ganzen gleichartig; ihr Aussehen wird von Abb. 2 veranschaulicht.

Elf bis dreizehn Tage nach der ersten Röntgenaufnahme wurden die Tiere von neuem photographiert. Das Gewicht der Versuchstiere war da in sämtlichen Fällen niedriger als das der Kontrollen. Die Skelettentwicklung im linken Hinterbein lässt an diesem Zeitpunkt in allen vier Würfen einen deutlichen Unterschied zwischen Kontroll- und Versuchstieren erkennen. Die



Abb. 3. Dreizehn Tage alte Kaninchen. a. 16 ml Thyranon.  
b. Kontrolle.

letzteren weisen in sämtlichen Fällen eine weiter vorgeschrittene Verknöcherung auf (Abb. 3 und 4).

Ausnahmslos sind bei den Versuchstieren die distale Femurepiphyse sowie die proximale und distale Tibiaepiphyse besser entwickelt als die entsprechenden Knochenabschnitte der Kontrollen. Die Form der Femurkondylen ist bei den Versuchstieren deutlich erkennbar, bei den Kontrollen aber viel schlechter oder überhaupt nicht. Das Verhalten der proximalen Fibulaepiphyse veranschaulicht aufs beste die vorgeschrittene Verknöcherung bei den Versuchstieren. In den Röntgenbildern von den Kontrolltieren fehlt diese Epiphyse, oder sie ist nur als ein kleiner, schwacher, rundlicher Schatten sichtbar; bei den Versuchstieren dagegen tritt sie scharf in charakteristischer dreieckiger Form hervor. Auch im Tarsus findet man denselben Sachverhalt. Bei den Versuchstieren haben Os naviculare und Os cuboideum mehr oder weniger ausgeprägt die für ältere Tiere typische Gestalt, und bei wenigstens einem Wurf sieht man bei den Versuchstieren das Os cuneiforme II, nicht aber bei den Kontrollen.

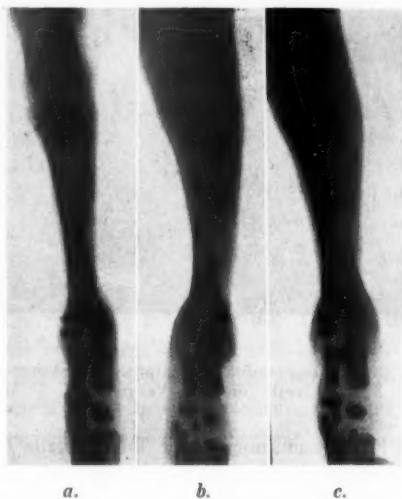


Abb. 4. Achtzehn Tage alte Kaninchen. *a.* 20 ml Thyranon.  
*b.* und *c.* Kontrolle.

Die Röntgenbilder des linken Hinterbeins wurden leider nicht von vornherein mit Rücksicht auf eine Messung der Knochenlänge aufgenommen, und das Material gestattet daher in dieser Beziehung keine sicheren Schlussfolgerungen. Man hat jedoch den Eindruck, als ob die Länge der Tibia bei den behandelten Tieren an dem Zeitpunkt, wo eine vorgeschrittene Verknöcherung deutlich nachweisbar ist, nicht von derjenigen der Kontrolltiere abweicht.

Bei einem Wurf konnten zwei Versuchstiere (und zwei Kontrollen) ungefähr vierzehn Tage länger am Leben erhalten werden als die übrigen, und sie bekamen während dieser Zeit noch 8 ml Thyranon bzw. 2 ml Thyroxin. Diese Tiere zeigten gegenüber den Kontrollen eine noch grössere Abweichung im Gewicht als die Würfe, wo die Tiere unmittelbar getötet worden waren, nachdem sich die vorgeschrittene Verknöcherung hatte feststellen lassen, und die Tibia der Versuchstiere ist hier deutlich kürzer als die der Kontrollen. Das Material ist naturgemäss nicht gross genug, um einen generellen Rückschluss zu ermöglichen.

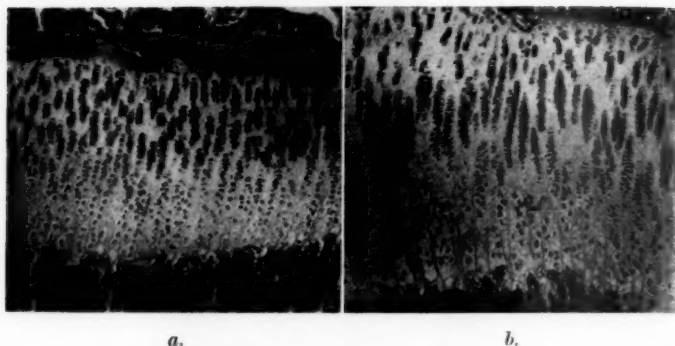


Abb. 5. Schnitt durch die distale Tibiaepiphyse. *a.* Versuchstier. *b.* Kontrolle (dieselbe Vergr.).

Der distale Epiphysenknorpel der Tibia wurde bei sechs Versuchstieren histologisch untersucht und mit dem von sechs Kontrolltieren verglichen. Bei den behandelten Tieren war der Knorpel in sämtlichen Fällen schmärer als bei den unbehandelten (Abb. 5).

Was die einzelnen Zonen des Epiphysenknorpels betrifft, so macht sich die Breitenabnahme am deutlichsten in dem Gebiet bemerkbar, welches von den wuchernden Zellen eingenommen wird (in der Pfeilerzone). Die Pfeilerzone besteht also aus einer kleineren Anzahl von Zellen. Im Bereich des hypertrophischen blasigen Knorpels ist die Verschmälerung unsicher, es hat aber den Anschein, als seien die Zellen in dieser Partie bei den behandelten Tieren kleiner. Das histologische Bild spricht mithin am ehesten für eine verminderte Aktivität innerhalb des Epiphysenknorpels. An der Diaphyse ergaben sich keine sicheren histologischen Differenzen zwischen Versuchs- und Kontrolltieren, ausser in einem Fall. Dieses Tier hatte Thyroxin während etwas längerer Zeit erhalten als die übrigen; die Knochenbälkchen in der Diaphyse lassen hier das Osteoblastem vermissen, und die Zwischenräume zwischen den Bälkchen sind mit einem lockeren fibrösen Gewebe ausgefüllt.

*Erörterung.*

Unter den Problemen, welche mit der kindlichen Hyperthyreose verknüpft sind, kommt dem Längenwachstum und der Skelettentwicklung nicht nur ein klinisch-diagnostisches, sondern auch ein allgemeines biologisches Interesse zu. Studien über dieses verhältnismässig seltene Leiden können sicherlich zum Verständnis der verschiedenen endokrinen Faktoren beitragen, deren Einfluss das Wachstum unterstellt ist, und Einblick in den hiermit verknüpften Fragenkomplex gewähren. Die klinischen Erfahrungen liefern am ehesten einen Beleg für die Ansicht, dass Kinder mit Hyperthyreose besonders hochwüchsig sind. Auf der anderen Seite sind Fälle beschrieben worden, wo die Körpergrösse das Normalmass nicht erreichte. Beobachtungen einer über die Norm hinaus vorgeschrittenen Verknöcherung bei kindlicher Hyperthyreose sind freilich recht dünn gesät, doch andererseits so übereinstimmend, dass es gerechtfertigt sein dürfte, diese Erscheinung für ein charakteristisches Symptom zu halten. Längenwachstum und Verknöcherung sind indessen, schematisch betrachtet, zwei voneinander getrennte Phänomene, von denen das erstere von der Zellwucherung, das letztere von der Zelldifferenzierung und -reifung abhängt. Diese Prozesse brauchen nicht parallel zu gehen und können sicher jeder für sich von verschiedenen Faktoren beeinflusst werden. Tierversuche, bei welchen man Schilddrüsenhormon zuführt, und die klinische Hyperthyreose lassen sich selbstverständlich nicht ohne weiteres miteinander vergleichen, es liegt aber nahe, sich im Hinblick auf die Ergebnisse jener Versuche (M. M. HOSKINS 1927, Verf.) die vorgeschrittene Skelettentwicklung bei kindlicher Hyperthyreose als eine Schilddrüsenwirkung vorzustellen. Es ist die Frage, ob sich auch die verschiedenen Beobachtungen über das Längenwachstum miteinander vereinbaren und auf einen Schilddrüseneffekt zurückführen lassen. Gewisse tierexperimentelle Feststellungen (DOTT 1923, M. und R. SILBERBERG 1938 und 1941) könnten hierfür sprechen. Es hat nämlich den Anschein, als liesse sich durch geeignete Dosierung eine temporäre Wachstumssteigerung erzielen, die jedoch durch einen zu schnell eintretenden



Reifungsprozess frühzeitig abgebrochen wird. Das Endresultat ist da ein Individuum von normaler Grösse.

Ob das Schilddrüsenhormon direkt auf die Knochenentwicklung einwirkt, oder ob dies auf dem Umwege über die Hypophyse bzw. andere innersekretorische Organe geschieht, ist eine Frage, auf die hier nicht eingegangen werden kann.

### **Zusammenfassung.**

Verf. legt dar, dass die Ansichten im Schrifttum über die Körpergrösse bei Kindern mit Hyperthyreose geteilt sind. Am häufigsten wird der Standpunkt vertreten, dass diese Kinder ungewöhnlich hochwüchsig sind. Die klinischen Beobachtungen über die Skelettentwicklung bei der kindlichen Hyperthyreose sind zwar spärlich, stimmen aber im grossen und ganzen miteinander überein: es besteht eine die Norm überschreitende Verknöcherung, die indessen an sich nicht eine Steigerung des Längenwachstums zu bedeuten braucht.

Verf. hat einige Tage alten Kaninchen grosse Dosen von Thyranon (Pharmacia) bzw. Thyroxin (Roche) subkutan injiziert und binnen vierzehn Tagen röntgenologisch bei den Versuchstieren eine im Vergleich zu derjenigen bei Kontrolltieren aus denselben Würfen vorgeschrittene Verknöcherung nachweisen können. Das Ergebnis steht im Einklang mit ähnlichen, von M. M. HOSKINS (1927) gemachten Feststellungen. Ferner wurde der distale Tibiaepiphysenknorpel histologisch untersucht, und Verf. hat, wie BIRCHER (1910), DOTT (1923) u. a., gefunden, dass der Epiphysenknorpel bei den behandelten Tieren schmaler ist, was auf eine verminderte Zellwucherung hindeutet.

Verf. hält die vorgeschrittene Verknöcherung bei der klinischen und experimentellen Hyperthyreose infantiler Individuen für den Ausdruck eines stimulierenden Einflusses der Schilddrüse auf die Differenzierungs- und Reifungsvorgänge im Bereich des Knochengerüsts.

Verf. gestattet sich, seinen Dank für Rat und Hilfe Herrn Professor A. WALLGREN und Herrn Professor H. BERGSTRAND

auszusprechen, sowie der Aktiengesellschaft Pharmacia, von der das Präparat Thyranon in überaus dankenswerter Weise zur Verfügung gestellt wurde.

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## **The Duration of Physiological Icterus Neonatorum.**

By

**BERNHARD BESKOW.**

Jaundice is a common but not constant phenomenon during the neonatal period. Through YLPPÖ's and ADA HIRSCH's investigations it became known that even the blood of the umbilical cord of all new-born infants has a higher bilirubin content than the blood of older children or adults. All newly born infants thus have hyperbilirubinaemia. This hyperbilirubinaemia subsequently increases in all, reaching a maximum on the second to fourth day and then gradually declining. Although a manifest skin and mucous-membrane jaundice does not appear in all the new-born, they all have, in essentials, a blood jaundice. The hyperbilirubinaemia is practically always more pronounced in children with manifest jaundice than in those without. For clinical jaundice values between 5 and 9 mg. per 100 c. c. are usually given. YLPPÖ found that from the height of the bilirubin level in the umbilical blood it can be decided with a high degree of probability whether visible jaundice will appear or not.

The question of the genesis of icterus neonatorum has been treated extensively in the literature and many different theories have been advanced. It is not my intention here to go further into these, but merely to discuss the question of how long physiological icterus usually lasts. On this point the statements in the literature are either very vague or are in conflict with one another. In »Nordisk Lærobok i Pediatik» LICHTENSTEIN writes that the discoloration disappears at the end of the first week of life or not later than in the course of the second. It is further stated that in high-grade jaundice the child becomes somewhat

drowsy and difficult to wake up for meals but that there are no other disturbances in the state of health. In Pfaundler and Schlossman's »Handbuch der Kinderheilkunde» VON REUSS contends, however, that it is often difficult to distinguish the physiological types of icterus neonatorum from the pathological. In Brennemann's »Practice of Pediatrics» AMBERG states that the duration of icterus neonatorum is usually two to three days and sometimes eight to ten days. If it is of longer duration the condition is called icterus neonatorum prolongatus, »which is contracted almost solely by premature children». YLPPÖ states that the yellow coloration may last so long as 10 to 14 days. If the coloration lasts over 14 days, he calls it icterus prolongatus, and this is usually found in premature infants. However, many pediatricists are probably of the opinion that physiological icterus can have a still longer duration. The yellow coloration may be judged differently, the observations may vary in exactness, the season and the illumination may play a part, electric light, for instance, always giving a fewer number of jaundice cases, and so on. This may also account for the divergent statements as to the frequency of jaundice. YLPPÖ found 82 % icteric children, HIRSCH about 80 %, DAVIDSON et al. about 50 %, WAUGH about 30 %, and UNGER about 20 %.

#### *Personal Investigations.<sup>1</sup>*

At the suggestion of my Chief, Dr. Y. Åkerrén, I have made a study of the duration of icterus neonatorum. The material underlying this study consists of all the infants born during the period July 6—Sept. 6, 1944, at the Women's Clinic in Gothenburg (to the Head of the Clinic, Prof. E. Jerlov, I am greatly indebted for permission to conduct my investigation there). These children were all examined with regard to the presence or absence of visible jaundice, in the great majority of cases by me personally and in the other cases by nurses familiar with the care of the

<sup>1</sup> The statistical reduction of the material has been kindly undertaken by Professor GUNNAR DAHLBERG, Uppsala, to whom I hereby tender my cordial thanks.

newly born. Each infant was examined twice daily in full daylight. Since being discharged from the Women's Clinic, which as a rule took place on the 7th or 8th day of life, the children who were still jaundiced at the time of discharge have been followed up through the respective Children's Welfare Centre. In certain cases they have been examined at the Children's Hospital. Most of the children were also examined daily in daylight after being discharged from the maternity institution. Those who did not exhibit any signs of jaundice on being discharged were not followed further. Should a jaundice have appeared in them later, it cannot in any case be a question of a physiological icterus neonatorum. The total number of children born alive during the period the investigation was in progress was 949. Of these, three have dropped out, viz. two cases of icterus neonatorum gravis (typical Rhesus system cases) and one that was not accessible for subsequent control. There thus remain 946 cases, 476 of which were boys and 470 girls. Of these, 607 have shown jaundice, which gives a frequency of  $64.16 \pm 1.56\%$ .

The children exhibiting physiological jaundice have been divided into three groups.

Group I. Cases with very mild jaundice that disappeared within the course of at most 48 hours. This jaundice is often concealed by the red skin colour of the new-born and can only be registered with certainty after anemization of the skin. Frequently it occurs only on the upper half of the body. A jaundice of this mild type occurred in 316 cases ( $= 33.40 \pm 1.53\%$ ).

Group II. Cases of jaundice having a duration of 2 to 14 days.

Group III. Cases of icterus prolongatus, i. e. having a duration of at least 14 days.

For the sake of lucidity the most important of the data emerging from the investigation have been tabulated.

Table 1 shows the percentage distribution within different weight groups of the icterus neonatorum cases belonging to groups II and III according to the above division. The table shows an especially high frequency of icterus of more than 48 hours' standing among the lowest weight class, the premature. The difference in frequency of jaundice lasting at least 48 hours

Table 1.

Percentage number of cases of icterus neonatorum belonging to groups II and III.

Birth-weight in gm	Boys			Girls			Both sexes		
	Number born	of which with ict.	% with ict.	Number born	of which with ict.	% with ict.	Number born	of which with ict.	% with ict.
Under 2 500	18	16	$88.89 \pm 7.41$	21	16	$76.19 \pm 9.29$	39	32	$82.05 \pm 6.15$
2 510—3 000	42	10	$23.81 \pm 6.57$	63	24	$38.10 \pm 6.12$	105	34	$32.38 \pm 4.57$
3 010—3 500	126	45	$35.71 \pm 4.27$	153	44	$28.76 \pm 3.66$	279	89	$31.90 \pm 2.79$
3 510—4 000	196	59	$30.10 \pm 3.28$	162	35	$21.60 \pm 3.23$	358	94	$26.26 \pm 2.33$
4 010— $\infty$	94	29	$30.85 \pm 4.76$	71	13	$18.31 \pm 4.59$	165	42	$25.45 \pm 3.89$
Total	476	159	$33.40 \pm 2.16$	470	132	$28.09 \pm 2.07$	946	291	$30.76 \pm 1.50$

<sup>1</sup> 1 boy and 2 girls have dropped out.

between the group with a birth-weight below 2 500 grams and the group with a birth-weight above 2 500 grams is  $53.49 \pm 6.32\%$  and is thus statistically highly significant. This observation confirms the old experience that jaundice is often very distinctly pronounced and also long-standing in premature children and those with a low birth-weight. A comparison between the other weight groups among themselves nowhere shows statistically significant or even probable differences in regard to the frequency of jaundice.

Table 2 shows the average age in days for the occurrence of jaundice within groups II and III. Evidently jaundice becomes visible somewhat earlier in children with a low birth-weight than in the rest. A statistical comparison shows that the difference in the average age at which visible jaundice occurs as between the weight group under 2 500 grams and the groups 2 510—3 000 and above 4 000 grams amounts to  $1.2 \pm 0.22$  days of twentyfour hours. Thus, the difference is significant. The same also applies to the lowest weight group compared with the remaining groups.

Table 2 b shows the average age at which jaundice appears in group III, i. e. cases of icterus prolongatus. Here, too, the condi-

Table 2 a.

Average age in days when icterus appeared (incl. icterus prolongatus) belonging to groups II and III.

Birth-weight gm	Boys			Girls			Both sexes		
	n	$M \pm \epsilon(M)$	$\sigma$	n	$M \pm \epsilon(M)$	$\sigma$	n	$M \pm \epsilon(M)$	$\sigma$
Under 2 500	16	$1.6 \pm 0.2$	0.78	16	$1.7 \pm 0.2$	0.77	32	$1.7 \pm 0.1$	0.63
2 510—3 000	10	$2.6 \pm 0.4$	1.35	24	$3.0 \pm 0.2$	1.00	34	$2.9 \pm 0.2$	1.06
3 010—3 500	45	$3.1 \pm 0.1$	1.05	44	$3.0 \pm 0.2$	1.06	89	$3.0 \pm 0.1$	1.19
3 510—4 000	59	$3.1 \pm 0.1$	1.17	35	$3.0 \pm 0.2$	1.13	94	$3.1 \pm 0.1$	1.04
4 010— $\infty$	29	$3.0 \pm 0.3$	1.89	13	$2.7 \pm 0.2$	0.82	42	$2.9 \pm 0.2$	1.25
Total	159	$2.9 \pm 0.1$	1.23	132	$2.8 \pm 0.1$	1.12	291	$2.9 \pm 0.1$	1.06

Table 2 b.

Average age in days when icterus prolongatus appeared. Both sexes.

Birth-weight gm	n	$M \pm \epsilon(M)$	$\sigma$
Under 2 500	19	$1.6 \pm 0.1$	0.64
2 510—3 000	9	$2.2 \pm (0.3)$	(0.99)
3 010—3 500	22	$2.4 \pm 0.2$	0.88
3 510—4 000	17	$2.4 \pm 0.1$	0.61
over 4 000	13	$2.4 \pm 0.2$	0.82
Total	80	$2.2 \pm 0.1$	0.79

tion appears earliest in the group with a birth-weight below 2 500 grams. The difference between this group and the groups with birth-weights of 3 010—3 500, 3 510—4 000 grams and above 4 000 grams respectively (the group between 2 510 and 3 000 grams is too small for statistical treatment) amounts to  $0.8 \pm 0.22$  days. The difference is statistically significant.

Table 3 gives the average duration in days for jaundice belonging to groups II and III. The premature children show a longer duration than all the other groups. The difference between



Table 3.

Duration of icterus in days within groups II and III.

Birth-weight gm	Boys			Girls			Both sexes		
	<i>n</i>	$M \pm \epsilon(M)$	$\sigma$	<i>n</i>	$M \pm \epsilon(M)$	$\sigma$	<i>n</i>	$M \pm \epsilon(M)$	$\sigma$
Under 2 500	16	$16.56 \pm 1.63$	6.53	16	$15.13 \pm 1.71$	6.86	32	$15.84 \pm 1.17$	6.63
2 510—3 000	10	$15.40 \pm (2.65)$	8.37	24	$10.38 \pm 1.13$	5.55	34	$11.35 \pm 1.16$	6.78
3 010—3 500	45	$10.58 \pm 0.79$	5.27	44	$10.68 \pm 1.05$	6.96	89	$10.63 \pm 0.65$	6.10
3 510—4 000	59	$10.69 \pm 0.69$	5.31	35	$9.17 \pm 0.63$	3.73	94	$10.13 \pm 0.50$	4.82
4 010— $\infty$	29	$11.52 \pm 1.41$	7.61	13	$12.77 \pm 1.44$	5.20	42	$11.90 \pm 1.07$	6.92
Total	159	$11.70 \pm 0.50$	6.35	132	$10.97 \pm 0.52$	5.99	291	$11.37 \pm 0.36$	6.20

the group with a birth-weight below 2 500 grams and the group with a birth-weight of 2 510—3 000 grams is, however, not statistically significant but probable ( $4.40 \pm 1.65$  %). Between the group under 2 500 grams and the 3 010—3 500 grams group the difference is  $5.21 \pm 1.34$  %, between the group under 2 500 and the 3 510—4 000 grams group it is  $5.71 \pm 1.27$  %, and between the group under 2 500 and that from 4 010 upwards it is  $3.94 \pm 1.22$  %. All these differences are statistically significant.

Table 4 gives the frequency of icterus prolongatus (group III) in relation to the total number of jaundice cases having a duration of at least 48 hours (groups II and III together). Here, too, the lowest weight group shows the highest frequency of prolonged jaundice. The difference between the frequency of icterus prolongatus in the group with a birth-weight below 2 500 grams and the other groups aggregated  $35.8 \pm 9.2$  %, thus being statistically significant. A comparison between the other weight groups amongst themselves discloses no significant or even probable difference anywhere.

Table 4 b shows the frequency of icterus prolongatus (group III) for the whole material. The total frequency amounts to  $8.46 \pm 0.90$  % (80 cases among 946). If the lowest weight group, the premature, is disregarded, the frequency of icterus prolongatus in this series amounts to  $6.73 \pm 0.83$  % (61 among 907). The

Table 4 a.

Percentage number of cases of icterus neonatorum in which icterus lasted at least 14 days (icterus prolongatus).

Birth-weight gm	Boys			Girls			Both sexes		
	Number of cases	of which ict. prol.	% ict. prol.	Number of cases	of which ict. prol.	% ict. prol.	Number of cases	of which ict. prol.	% ict. prol.
Under 2 500	16	10	$62.5 \pm 12.1$	10	9	$56.3 \pm 12.4$	32	19	$59.4 \pm 8.7$
2 510—3 000	10	5	$50.0 \pm 15.8$	24	4	$16.7 \pm 7.6$	34	9	$26.5 \pm 7.6$
3 010—3 500	45	11	$24.4 \pm 6.4$	44	11	$25.0 \pm 6.5$	89	22	$24.7 \pm 4.6$
3 510—4 000	59	13	$22.0 \pm 5.4$	35	4	$11.4 \pm 5.4$	94	17	$18.1 \pm 4.0$
over 4 000	29	8	$27.6 \pm 8.8$	13	5	$38.5 \pm 13.5$	42	13	$31.0 \pm 7.1$
Total	159	47	$29.6 \pm 3.6$	132	33	$25.0 \pm 3.8$	291	80	$27.5 \pm 2.6$

Table 4 b.

Frequency of icterus prolongatus in the whole material.

Birth-weight in gm	Number of cases	of which ict. prol.	% ict. prol.
Under 2 500	30	19	$48.72 \pm 8.00$
2 510—3 000	105	9	$8.57 \pm 2.53$
3 010—3 500	279	22	$7.89 \pm 1.62$
3 510—4 000	358	17	$4.75 \pm 1.12$
4 010— $\infty$	165	13	$7.81 \pm 2.00$
2 510— $\infty$	907	61	$6.73 \pm 0.83$
Total	946	80	$8.46 \pm 0.90$

frequency of icterus prolongatus is higher among children with the lowest birth-weight than among the others. The difference between these two groups is  $41.99 \pm 8.04$  % and is thus significant. On the other hand, a comparison between the other weight groups amongst themselves with respect to the frequency of icterus prolongatus shows good statistical agreement. With reference to the number

Table 5 a.

Initial decrease in weight (in grams). Normal material = children, clinically healthy, who have not had icterus and not had a birth-weight below 2500 grams.

Sex	Initial decrease in weight		
	<i>n</i>	$M \pm \epsilon(M)$	$\sigma$
Boys . . . . .	25	$150 \pm 19$	94
Girls . . . . .	25	$104 \pm 23$	116
Both sexes . . . . .	50	$127 \pm 15$	106

of days that visible jaundice was observed within group III, 7 of the premature infants showed a duration of between 14 and 20 days and 12 a duration between 20 and at most 30 days. Among children with birth-weights above 2500 grams, 35 showed a duration of between 14 and 20 days and 24 a duration of between 20 and 30 days. A duration of jaundice exceeding 30 days has only been shown by 2 cases. The longest amounted to 37 days.

Table 5 a indicates the initial fall in weight in grams among children with icterus neonatorum and belonging to groups II and III. Table 5 b shows the extent of the initial fall in weight within a control group of 50 children who had not exhibited jaundice and who had a birth-weight of at least 2500 grams. A comparison shows that the initial weight drop averaged considerably more among icteric children belonging to groups II and III than among non-icteric children. A statistical comparison shows a difference of  $122 \pm 16.55$  grams. The difference between the jaundice cases and the control material is thus statistically significant. If account is also taken of the fact that groups II and III include cases of low birth-weight under 2500 grams, with a consequent comparatively insignificant absolute fall in weight, it becomes obvious that the occurrence of icterus neonatorum with a duration exceeding 2 days is correlated to the size of the initial fall in weight.

Table 5 c gives the size of the initial fall in weight for children

Table 5 b.

Mean of initial weight losses in children with icterus neonatorum, distributed by birth-weight within groups II and III.

Birth-weight gm	Boys			Girls			Both sexes		
	n	$M \pm \epsilon(M)$	$\sigma$	n	$M \pm \epsilon(M)$	$\sigma$	n	$M \pm \epsilon(M)$	$\sigma$
Under 2 500	16	$189 \pm 21$	85	16	$168 \pm 20$	78	32	$178 \pm 14$	81
2 510—3 000	10	$154 \pm 30$	96	24	$174 \pm 26$	126	34	$168 \pm 20$	117
3 010—3 500	45	$245 \pm 10$	70	44	$243 \pm 11$	76	89	$244 \pm 8$	72
3 510—4 000	59	$268 \pm 19$	144	35	$271 \pm 13$	75	94	$269 \pm 13$	122
over 4 000	29	$324 \pm 17$	91	13	$358 \pm 26$	92	42	$335 \pm 14$	91
Total	159	$257 \pm 9$	117	132	$240 \pm 9$	103	291	$249 \pm 7$	111

Table 5 c.

Mean of initial weight loss (in grams) in children with icterus neonatorum prolongatus.

Sex	n	$M \pm \epsilon(M)$	$\sigma$
Boys . . . . .	47	$237 \pm 24$	166
Girls . . . . .	33	$257 \pm 18$	104
Both sexes . . . . .	80	$245 \pm 16$	142

belonging to group III, i. e. with icterus prolongatus. This averages  $245 \pm 16$  grams. As is seen, it does not differ notably from the aggregate mean of groups II and III (Table 5 a).

#### *The Prothrombin Index in Icterus neonatorum.*

All the children have been given vitamin K as a prophylactic measure in a dose of 1 mg. according to the rules worked out by LEHMANN. To see whether any signs of disturbance in hepatic function in respect of the behaviour of the prothrombin index on the second to third day of life could be found in children who

had developed icterus prolongatus, this time was determined in a series of cases. In 40 cases of jaundice of shorter duration than 14 days it was found to average 71, and in 64 cases of prolonged jaundice the average was 72. Thus, there is no difference in the prothrombin index and hence no evidence, either, that the side of liver function which has to do with prothrombin formation is disturbed in children in whom an icterus neonatorum prolongatus develops.

*On the Method of Determining the Icterus Index ad Modum Meulengracht in New-born Children.*

The serum for the determination of the icterus index in the newly born was obtained in the following manner. Capillary tubes about 80 mm. in length and 1.5 mm. in internal diameter, bent in the shape of a U are filled with blood obtained by puncturing the heel, a finger or a toe. All air must be kept excluded. The blood is allowed to coagulate a couple of minutes after withdrawal of the specimen, and the tubes are then centrifuged for a couple of minutes. It is advisable to loosen the upper edge of the clot before starting centrifugation. After centrifugation the clot has sunk to the bottom of the U-tube and the supernatant serum can be poured off. Thereupon the icterus index is determined according to Meulengracht's method by diluting with water until the serum assumes the same colour as an equally thick layer of the standard solution of potassium dichromate.

In the test series conducted here a number of random tests were made of the height of the icterus index on the third day of life. No sure difference could be detected between the height of the index in children that were subsequently found to exhibit a prolonged jaundice and those with icterus of more ordinary duration. I therefore refrain from giving detailed data of the individual cases.

*Discussion of the Results.*

The most important results of the investigation can be seen from the above report. That a jaundice which does not in any

way differ in its course from the ordinary icterus neonatorum except by a remarkably long duration of more than two weeks, in exceptional cases up to fully seven weeks, is not particularly rare stands forth in all desirable clearness. Most commonly this icterus prolongatus is found in children with a low birth-weight, below 2 500 grams, but it is not rare in children with birth-weights above 2 500 grams either. The statement sometimes found in the literature that if a jaundice persists for rather a long period of time after the true neonatal period this should excite a suspicion of some complication, or points to some other cause than the usual, is therefore probably unfounded on the whole. Only if the jaundice does not show a tendency to recede, or if it is combined with other and palpable signs of disease, need a suspicion of complication or actual disease arise. All the children embraced by this investigation have been clinically healthy.

Statistically, a significantly greater fall in weight evidently characterizes those children who develop a rather long-standing and pronounced icterus neonatorum than new-born children who do not exhibit icterus. This observation seems to me to be of some interest. It would also be of interest to examine the further course of the weight curve in children with or without distinct or fairly long-standing jaundice, but this meets with insurmountable practical difficulties, as the time after the discharge of the mother from the maternity institution is involved. Unfortunately, therefore, I cannot submit any reliable and comparable figures that permit any definite conclusions being drawn as to the differences in question in the course of the weight-increase curve after termination of the initial fall in weight in children with or without pronounced or long-standing jaundice. I shall merely mention that I have received a certain impression of a remarkably slow weight increase in those children who have had icterus prolongatus. It must, however, be pointed out that these gave the impression throughout of being hale and healthy. Supplementary feeding had in practically no case of icterus prolongatus been considered necessary.

What connexion can there be between the extent of the initial fall in weight and the tendency to long-standing jaundice? The

following possibilities may be conceived: 1. A rather pronounced inanition exercises an unfavourable effect on the hepatic function, this in its turn having the consequence that the physiological hyperbilirubinaemia recedes more slowly in these children than in others. 2. A disturbance of liver function is primary in both disturbances, viz, the relatively considerable fall in weight and the long duration of the jaundice. Arguments can undoubtedly be advanced in favour of these two interpretations. I refrain, however, from a closer discussion of these questions, as anything else but a hypothetical answer can scarcely be given.

### Summary.

A study is made of the duration of physiological icterus neonatorum in a group of apparently healthy children. The investigation is based on 946 children in all, 476 boys and 470 girls. Of these, 607 ( $64.16 \pm 1.56\%$ ) exhibited jaundice. Jaundice of longer duration than 48 hours and of rather distinct character occurred in a total of 291 children ( $30.76 \pm 1.50\%$ ). Statistically, this rather pronounced jaundice was more common in children with a low birth-weight than in children with normal birth-weight. Among children with a birth-weight below 2 500 grams it thus occurred in  $82.05 \pm 6.15\%$  of cases, among those with a birth-weight above 2 500 grams in  $28.56 \pm 1.46\%$ .

Jaundice appears somewhat earlier in children with a low birth-weight than in those with normal birth-weight.

The average duration of physiological jaundice lasting in general more than 48 hours has been  $11.37 \pm 0.36$  days in the present material. Children with a low birth-weight show, on an average, a longer duration of jaundice than children with birth-weights above 3 000 grams.

Icterus neonatorum prolongatus, i. e. icterus with a duration of at least 14 days, occurred in 80 cases out of the 946, which gives a frequency of  $8.46 \pm 0.90\%$ . Here, too, the frequency is incomparably highest in children with a birth-weight below 2 500 grams ( $48.72 \pm 8.00\%$ ). In children with birth-weights above 2 500 grams the corresponding frequency was  $6.73 \pm 0.83\%$ . Among

children with a low birth-weight, below 2 500 grams, jaundice lasted between 14 and 20 days in 7 cases and between 20 and 30 days in the remaining 12. Infants with birth-weights above 2 500 grams showed a duration of between 14 and 20 days in 35 cases, of between 20 and 30 days in 24 cases, and of more than 30 days in 2 instances. The longest duration observed was 37 days.

Children having a distinct and rather long-standing jaundice showed a, statistically verified, greater initial fall in weight than a control series with normal birth-weight and without visible jaundice.

A study of the behaviour of the prothrombin index after prophylactic administration of vitamin K on the second or third day of life showed no difference between cases with or without long-standing or distinct jaundice.

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## **Sulfanilamide Drugs and Acute Nephritis.**

By

**OLOF BRANDBERG.**

Our experience of the drawbacks of sulfanilamide treatment is extensive. Particularly alarming are the complications in the blood and the kidneys. Many reports of fatal cases of anuria have been published (BERGSTRAND, TALLROTH, *et al.*).

Despite these dangerous complications, we are often compelled to use sulfanilamide drugs, even in cases in which the risks of the treatment are patent. I refer here to acute septic infections combined with nephritis. In the cases of this kind which I have encountered, the condition was so malignant that a good outcome could hardly be expected without resource to chemotherapy. In this situation I have reasoned that the acute infection is the cause of the damage to the kidneys and that an effort must be made to combat the focal infection and thereby attempt to create better conditions for the healing of the nephritis. However, the tendency of the sulfanilamide drugs to harm the kidneys in cases of this kind must always be kept in mind.

The treatment of nephritis with sulfanilamide is not a new method. WILLIAMS, LONGCOPE and JANEWAY (1942) published 42 cases of nephritis treated with sulfanilamide; these showed a larger percentage of clinical recoveries than 72 control cases. BRENNING (1943) published two cases of nephritis associated with scarlatina. Here a severe throat infection was the indication for treatment with sulfathiazole, and in both cases the convalescence was exceedingly favorable and the nephritis regressed rapidly and completely.

Thirty-two cases of acute nephritis have been treated in this service from December 1943 to January 1945. None of the patients died. The disease ran a satisfactory course as a rule, but one or two of the patients still exhibit renal damage, despite protracted treatment.

Six of these 32 cases were submitted to chemotherapy. They are described in the following:

### *Case Reports.*

*Case 1* (Record No. 51: 1943). Otto J, aged six, previously healthy with irrelevant family history and three healthy siblings, fell ill suddenly about a week before admission with headache and general fatigue. His temperature was not taken, but he felt feverish. A few days later he improved and was allowed to go out. On December 1, 1943, headache set in again. This time a circumscribed swelling was noted on the right side of his neck, and the urine was red. On December 3 the diagnosis of acute nephritis was made by a physician, and the boy was referred to the hospital.

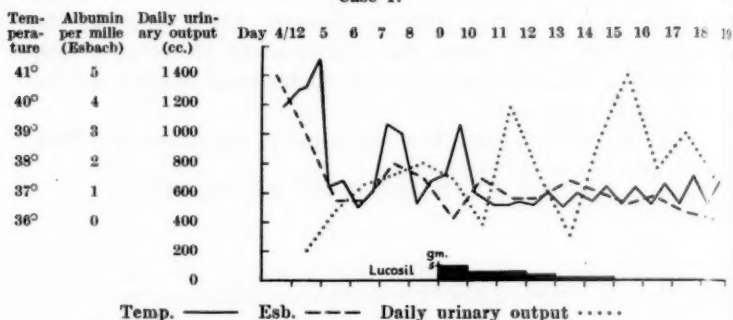
Examination on admission revealed a very ill, pale and apathetic child, no edema, no skin lesions, an inflamed gland the size of a walnut in the right angle of the jaw, and an inflamed and swollen throat. The urine was blood-stained, and Esbach's reagent showed an albumin content of 5 per mille; the sediment contained masses of red blood cells, many white blood cells and casts. The nonprotein nitrogen measured 54 mg. per hundred cubic centimeters, the blood pressure was 120 systolic and 60 diastolic, and the sedimentation rate was 70 mm. The morning temperature was 38.9 C. and the evening temperature 40.4 C. Swabs from the throat yielded hemolytic streptococci on culture.

At first the patient was only treated with a strict nephritic diet. A week after admission the condition grew worse due to the development of a peritonsillar swelling and bulging forward of the posterior pharyngeal wall. The daily values for nonprotein nitrogen were 84, 88, 84, 64, 68, and 69 mg. The daily urinary output rose from 200 to between 600 and 800 cc., but the urine remained blood-stained.

On January 10, 1944, treatment with the sulfanilamide compound Lucosil (Lundbeck) was begun with the initial dose of 1.5 + 1.5 Gm. and then 0.5 Gm. every fourth hour. On January 11 and 12, 0.5 Gm. was given every fourth hour, on January 13 0.5 Gm. every sixth hour, and the next two days 0.25 Gm. every sixth hour. Thus the patient received altogether 17 Gm. of Lucosil in the course of six days.

The day after the treatment was begun the temperature became normal and the inflammation in the throat receded; the cervical

## Case 1.



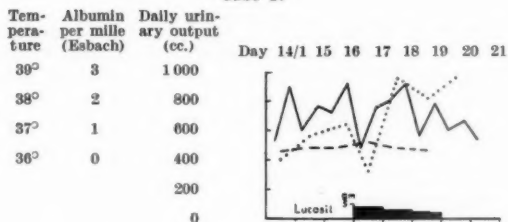
lymphoma soon vanished. The urinary output also improved, amounting to 1200 cc. on January 12 and 1400 cc. on January 16. The albumin diminished rapidly, only insignificant amounts being registered from January 19 on. The nonprotein nitrogen also diminished, amounting to 54 mg. on January 13, 40 mg. on January 17 and 39 mg. on January 23, and remained from then on between 28 and 40 mg. During the stay in hospital the patient contracted chickenpox; a phlegmon which developed afterward healed rapidly after incision. Shortly afterward rheumatic fever developed with joint pain and a cardiac murmur and fever from January 26 to February 3. The condition then improved. On February 17 bilateral tonsillectomy was performed.

The patient was discharged on March 11, after about three months in hospital. At that time there was no albumin in the urine and no signs of cardiac or articular disease. The sedimentation rate was 7 mm., and the sediment showed nothing of note.

**Summary.** A six-year-old boy contracted a severe throat infection with lymphadenitis and nephritis with nonprotein nitrogen values up to 84 mg. Since the condition seemed alarming and it was feared a pharyngeal abscess would develop, sulfanilamide (Lucosil) treatment was begun. The result was immediate regression of both the septicemia and the nephritis.

**Case 2 (Record No. 7: 1944).** Margareta B, aged nine, an only child, had been healthy apart from measles, chickenpox and mumps. Her mother and one maternal uncle had had tuberculosis. She fell ill on November 19, 1943, with fever but no local symptoms. She stayed in bed about two weeks until her temperature returned to normal and then began school again. A few days later she again grew feverish and this time she had a sore throat. Shortly before Christmas a peritonsillar

## Case 2.



abscess developed. It was lanced twice, and each time a large amount of pus was exuded. On December 23 the urine became dark red, and albuminuria was noted by the physician consulted. On January 3 the patient was referred to our hospital.

Examination on admission showed a pale and thin child, no edema, normal-looking throat, a short, harsh systolic murmur in the third left intercostal space, regular cardiac rhythm, blood pressure 140 systolic and 98 diastolic, normal lungs, abdomen and reflexes, and sedimentation rate 45 mm. The urinary albumin amounted to 3 per mille (Erbach's reagent) and the daily output was 300 cc.; the sediment contained many red blood cells and a few leukocytes. The nonprotein nitrogen amounted to 34 mg.

A nephritic diet led to improvement. The temperature became normal, the daily urinary output rose to 1400 cc., and the albumin fell to 0.3 to 0.4 per mille. The urinary sediment remained largely unchanged. On January 14 the temperature rose to 38.5 C. and the throat became red and swollen. On January 19 the lymph nodes in both angles of the jaw were seen to be greatly swollen. The albuminuria did not increase, however, and satisfactory amounts of urine were excreted. On January 18 it was feared that another peritonsillar abscess would develop and treatment with Lucosil was begun. First, two doses of 1 Gm. were given four hours apart, after which doses of 0.5 Gm. were given at four-hour intervals through the 19th and every six hours on the 20th. The treatment was discontinued on January 21, the patient having received altogether 9 Gm. of Lucosil.

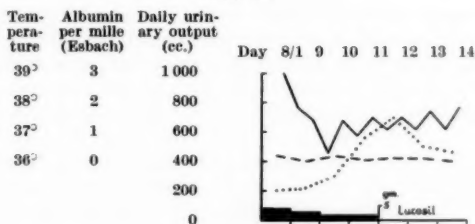
As soon as the treatment was begun, the temperature returned to normal. The subsequent course was uneventful. In the summer of 1944 tonsillectomy was done and the adenoids were also removed. Examination at the out-patient service afterward showed that the nephritis had healed completely.

**Summary:** A nine-year-old girl had nephritis following two attacks of quinsy. The nephritis appeared to regress satisfactorily. When a recurrence of the sore throat made it probable that a third peritonsillar

abscess would develop, treatment with the sulfanilamide drug Lucosil was begun and led to rapid recovery.

*Case 3* (Record No. 19/1944). Gunilla L., aged five, with irrelevant family history, had had measles, chickenpox and German measles, but had been healthy otherwise. On December 25, shortly after her sister had a catarrhal respiratory infection, she fell ill with fever. A few days later the cervical lymph nodes were swollen and tender. On January 8 nephritis was diagnosed, and lymph nodes the size of a pigeon's egg were seen in both angles of the jaw. There was also a large, bright red peritonsillar swelling. Nothing of note was seen in the internal organs. The albumin content of the urine was 0.2 per mille (Esbach's reagent); the sediment contained many red blood cells, a moderate amount of leukocytes and numerous granular casts. Nonprotein nitrogen measured 43 mg., the sedimentation rate was 41 mm., the temperature 39 C. and the blood pressure 120 systolic and 75 diastolic.

Case 3.



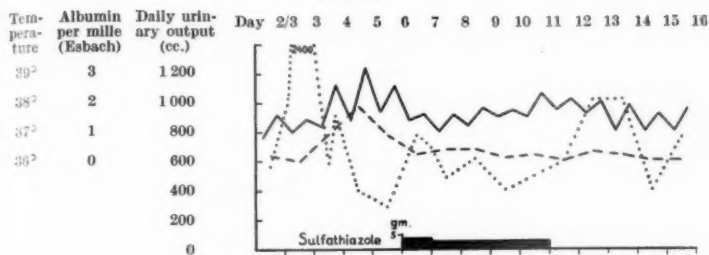
Because of the ugly infection of the throat and lymph nodes, which it was feared might lead to purulent liquefaction, treatment with Lucosil was begun. The patient was first given two doses of 1 Gm. for hours apart, then 0.5 Gm. every fourth hour and finally 0.5 Gm. every sixth hour. Altogether 11 Gm. of Lucosil were administered in the course of four days. The temperature dropped immediately to normal, the redness of the throat faded, and the swelling of the tonsils and lymph nodes subsided.

The subsequent course, followed at the out-patient service, was uneventful, and a complete cure resulted.

*Summary:* A five-year-old girl with ugly peritonsillitis and lymphadenitis together with nephritis was treated with the sulfanilamide Lucosil. The results was rapid regression of both the acute throat and glandular infection and of the nephritis.

*Case 4* (Record No. 118: 44). Gun H., aged eight, had had measles and chickenpox, but otherwise had been healthy, except for infection with intestinal worms. One of her three siblings had had tuberculosis.

## Case 4.



A physician was consulted on February 23, 1944, because of numerous small petechiae and bloody urine. Albuminuria was detected, and the child was referred to the hospital.

Examination on admission showed good general condition, normal throat, internal organs, and reflexes. No skin changes were visible then, nor any hemorrhages on the mucosal surfaces. There was no edema. The Hess and Rumpel-Leede capillary test caused no hemorrhages. The urine contained 1 per mille albumin (Esbach's reagent), and the sediment contained many red blood cells and a few leukocytes; the daily urinary output was 870 cc. The blood pressure was 125 systolic and 80 diastolic. The nonprotein nitrogen was 37 mg.

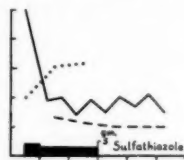
The first ten days at the hospital the course was favorable. On March 4, however, the temperature rose to 38.6 C., the patient vomited, innumerable petechiae developed all over the body, the throat became bright red and swollen, and there was a large admixture of blood in the urine.

Since the condition seemed alarming and quinsy was feared, sulfanilamide treatment was instituted. This time sulfathiazole (Astra) was employed; first two days with 1 Gm. every four hours and then 0.5 Gm. every four hours for five days. Altogether 16 Gm. of sulfathiazole were administered. The treatment resulted in an immediate drop in the temperature and general improvement. The nephritis seemed, if anything, favorably influenced by the treatment. The throat infection recurred several times, however, and finally tonsillectomy was performed. The nephritis was aggravated a few days after the operation, but afterward it vanished, and the patient was discharged healthy after three months and three weeks in hospital. Examination later at the outpatient service showed no trace of the nephritis.

*Case 5* (Record No. 193:44). Sten-Olof T., aged six, had an irrelevant family history. He had chickenpox and frequent sore throat and swelling of the cervical lymph nodes. He fell ill on March 27, 1944,

## Case 5.

Tem- pera- ture	Albumin per mille (Esbach)	Daily urin- ary output (cc.)	Day	3/4	4	5	6	7	8
39°	3	800							
38°	2	600							
37°	1	400							
36°	0	200							
		0							



with fever and sore throat. On March 30, swollen lymph nodes were observed in the left angle of the jaw. On April 1, the urine was red and was found to contain albumin and blood.

Examination on April 3 showed pallor, slight swelling of the face, trunk and extremities, a plum-sized, tender lymphoma in the left angle of the jaw, inflamed and swollen tonsils, normal-sized heart, a rough systolic murmur maximal over the apex, nothing else of note in the internal organs, normal reflexes, blood pressure 95 systolic and 70 diastolic, nonprotein nitrogen 33 mg., temperature 40.1 C., and 0.2 per mille albumin in the urine (Esbach's reagent).

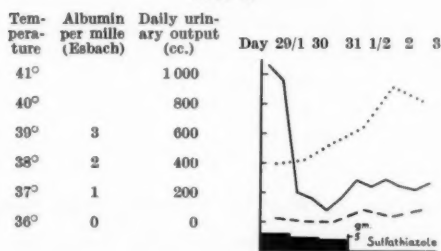
Despite the albuminuria, sulfanilamide treatment was begun because of the ugly throat and glandular infection. First two doses of 1 Gm. of sulfathiazole were given four hours apart and then 0.5 Gm. at four-hour intervals for three days, the patient receiving altogether 10 Gm. The temperature immediately dropped to normal, the throat and glandular infection rapidly subsided, and no effect on the kidneys could be noted.

*Case 6* (Record No. 46/1945). Birgit V., aged nine, had had albuminuria twice, first when she was two years old. She was admitted to the hospital on January 29, 1945, with high fever and pneumonia of rapid onset. Roentgenograms showed a pneumonic density in the basal posterior region of the right upper lobe.

There was slight swelling of the face but no other edema, no skin eruption or scaling. The heart and abdomen appeared normal, and nothing pathologic could be noted in the reflexes or the throat. There was slight swelling of the lingual papillae. Neurologic examination revealed nothing of note. The urine contained 4 per mille albumin (Esbach's reagent), and the daily output was 400 cc.; the sediment showed red blood cells, a few leukocytes, and a number of granular casts. The nonprotein nitrogen was 58 mg. The blood pressure was 110 systolic and 70 diastolic.

Because of the favorable experience in the former cases, sulfanilamide treatment was given for the pneumonia, despite the presence of nephritis. First two doses of 1.5 Gm. were given four hours apart,

## Case 6.



and then 0.75 Gm. every fourth hour, and finally every sixth hour. Altogether the patient received 13.5 Gm. The results of the medication were excellent in all respects. No effect on the kidneys was observed. In fact, the albumin vanished from the urine the days the sulfathiazole was given, and the urinary output remained around 600 cc. At the time of writing the child was still in hospital and in good condition, though the albumin content amounted to 4 per mille.

**Summary:** A nine-year-old girl with croupous pneumonia was treated with the sulfanilamide drug sulfathiazole, though she also had nephritis. No unfavorable effect on the nephritis was observed.

### Summary and Discussion.

Six cases of nephritis are described, in five of which an ugly throat infection and in one a croupous pneumonia led to treatment with the sulfanilamide compound Lucosil and sulfathiazole, respectively. All six cases ran a favorable course. Some hesitation was felt as to the wisdom of the treatment in view of the nephritis. However, the kidney disease regressed satisfactorily in all the cases. It is probably too much to hope that the nephritis regressed more rapidly than it would have done without chemotherapy. Yet it cannot be denied that the primary infection which accompanied the nephritis was cured, and in that way a favorable influence probably was exerted in the kidney disease.

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FROM THE PEDIATRIC CLINIC OF KAROLINSKA INSTITUTET AT KRON-  
PRINSESSAN LOVISA'S CHILDREN'S HOSPITAL, STOCKHOLM, HEAD: PROF.  
A. LICHTENSTEIN, AND THE WOMEN'S CLINIC, KAROLINSKA SJUKHUSET,  
STOCKHOLM, HEAD: PROF. A. WESTMAN.

## **The Treatment of Morbus Haemolyticus Neonatorum (Familial Erythroblastosis Foetalis).**

**Guiding Lines for Experiments towards an Improvement.**

By

**BIRGER BROMAN.**

The discovery of only a few years' standing that erythroblastosis foetalis is, in 90 % of the cases, caused by Rh incompatibility between mother and foetus has greatly increased the interest in this disease. It has subsequently been possible to show that the classical *familial* erythroblastosis foetalis is caused by such Rh incompatibility to even far more than 90 % (BROMAN 1944).

The discovery of the blood group system Rh therefore meant a tremendous step forward in the investigation of familial erythroblastosis foetalis or, to use a better name, morbus haemolyticus neonatorum. Investigations into this disease can nowadays hardly be considered satisfactory without a serological study of the cases in respect of the Rh system.

How, then, has the clinician profited from the results of research in this field appearing to date?

The possibility of serological investigation considerably facilitates *diagnosis*, which can nowadays be made more swiftly and with more certainty.

A serological investigation aimed at discovering the father's possible heterozygotism or homozygotism as regards the Rh character can sometimes *prognosticate* the risk of morbus haemolyticus neonatorum for future children in a given marriage.

As regards the *treatment*, the elucidation of the pathogenesis has meant that Rh-negative blood is nowadays used in blood transfusions to the affected child. Both American and English authors have shown that such blood survives considerably longer in the child's circulation than does Rh-positive blood.<sup>1</sup>

Certain authors have also reported that the introduction of transfusion with Rh-negative blood has resulted in a materially lower mortality among children suffering from morbus haemolyticus neonatorum than was previously the case, and it has even been stated that »if an infant with haemolytic disease of the newborn lives long enough to reach hospital, there is a good chance of its survival» (GIMSON 1943). On the other hand, so optimistic an attitude has been elsewhere (BROMAN 1944) criticised, and shown to depend on the fact that the author in question based her view on a selected material. The intrauterine cases of death, and cases of death during an apparently toxic condition, often with cerebral lesions, some days after birth, contribute materially to the mortality from this complaint. Severe cases of this kind cannot be expected to be saved only by Rh-negative transfusions, however early they may be made.

What ways have hitherto been considered for further improving our results?

An attempt can be made to exhaust or block the reticulo-endothelial system in the pregnant woman, which system may be thought to form Rh antibodies (BROMAN 1944, LEVINE 1944). In one case, an attempt at an exhaustion of this kind has also been made by daily intravenous administration of the husband's blood to the pregnant wife, without perceptible clinical advantage (BROMAN 1944). Great difficulties are also encountered in such treatments, since their effect cannot be measured by titrations *in vitro* of anti-Rh agglutinin. The strength of this agglutinin *in vitro* is, as is known, no reliable gauge of the degree of the influence on the foetus.

It should be possible to give the pregnant woman a hapten, able to neutralise or bind Rh antibodies without simultaneously

<sup>1</sup> Here the author leaves out of account the few cases of immunisation to the Rh-negative factor accompanied by agglutinin of the type anti-Hr or St.

stimulating the formation of new ones, in the hope of preventing the occurrence of morbus haemolyticus in the child (WIENER 1944). Unfortunately, however, we have as yet no such happen.

Thus, despite the knowledge of the pathogenesis, a rational therapy for morbus haemolyticus neonatorum has not been reached. The improvement of the symptomatic therapy which is contained in the use of Rh-negative blood is incontestable, but must not be overestimated. It is hardly likely that an improvement of this kind can radically affect the total mortality from the complaint (intrauterine+extrauterine cases of death).

Yet further practical attempts at improving the treatment in morbus haemolyticus neonatorum thus seem highly desirable. Working on hitherto known facts as to the disease, the author has therefore instituted such attempts, and the principles for them will be briefly given here.

An Rh-immunisation of the mother, proceeding during pregnancy, and a continual flooding of the child's organism with Rh antibodies, should impart lesions to the foetus at varying times before delivery, and not as a rule only after delivery. Admittedly, a number of foetuses from Rh-immunised women die *in utero*, and there still seem to be no sufficiently extensive and authoritative investigations to judge to what percent this happens. It nevertheless seems difficult to explain why a large number of children are unaffected up to partus, and then suddenly fall ill. As regards this, it is natural to assume some kind of protective mechanism for the child *in utero*, which ceases to function after birth. Theoretically, a mechanism like this must be thought to imply that the Rh antibodies in the mother's blood are prevented from acting on the organism of the child. Two different possibilities readily present themselves.

- 1) The placenta constitutes a protective barrier through which the Rh antibodies are unable to penetrate to the circulation of the child. Only in exceptional cases of placental changes, or more regularly in association with labour and the contraction of the uterus, do purely mechanical conditions set up a connection between the circulations of mother and child. This would mean that partus was the very function by which Rh antibodies are trans-

ferred to the child's circulation, so that they are as a rule only able to affect the child after this event.

A theory of this kind does not seem very probable, but if it were correct, a caesarean section before labour set in might be expected to constitute a prophylactically therapeutic operation for the child.

2) The mother's circulation contains a substance which passes through the placenta and prevents Rh antibodies from exerting their deleterious influence in the organism of the child. This protection decreases towards the end of pregnancy, and ceases with partus. The protective substance then disappears more quickly from the child's organism than do the Rh antibodies, which thereupon harm it. Proceeding from an argument of this kind, there seems reason to assume that the blood of pregnant women contains an inhibitory factor, active against Rh antibodies and possibly of hormonal nature. Such an inhibitory factor must be assumed present in abundance during the greater part of pregnancy, to decrease in the weeks before delivery to such a degree that its protective action wholly or in part ceases. This would explain why the children usually fall ill around, and in most cases not until after, partus.

To obtain an idea of the value of these theories, one should try to collect and follow a material of Rh-immunised mothers, who have previously had children with morbus haemolyticus neonatorum, and who are again pregnant. A caesarean section should be made before term, to see whether the disease can be prevented in the child by an operation of this kind.

Furthermore, by way of experiment, a hormone or some other substance which might possibly be thought to constitute the desired protective substance — possibly some combination of hormones — should be given to children with morbus haemolyticus neonatorum immediately after birth, and subsequently every day. If the blood values of the child are thereby affected, so that a progressive anaemia is checked, and if this seems to happen in several different cases, similar treatment should also be tried out on the Rh-immunised mothers during pregnancy, particularly in those cases where the mother has already had one or more fetuses

dying *in utero*. Severe cases of this kind are the true touchstone for a method of treating morbus haemolyticus neonatorum.

Investigations on the above lines are at present in progress, but are still far from completed. The material will be presented fully at a later date; here, the author will only give some indications of the results obtained hitherto.

The question as to whether a caesarean section before the onset of labour provides any protection to the child of an Rh-immunised woman can be answered in the negative here and now. The results of the investigations are in this respect so uniform that they must be regarded as final.

The attempt has been made to treat children with morbus haemolyticus neonatorum and Rh-immunised mothers with progesterone. To begin with, treatment of the children with 3—9 mgm of progesterone daily seemed to show a perceptible haemolysis-inhibiting effect in several consecutive cases. In later cases, however, it was found that this kind of effect was not seen regularly. These attempts nevertheless seem worth continuing. The attempts to protect the child *in utero* via the mother by giving her progesterone injections during pregnancy seemed to yield still less certain results. Here, however, there was the additional difficulty of giving the mother large doses of progesterone over quite a long time, and dosage questions may materially have influenced the uncertain effect.

Finally, it might be appropriate to point to an observation made during these experiments. The decline in the child's general condition, with increasing jaundice and possible rise in N. P. N. usually setting in during the hours and days immediately after birth, does not as a rule seem materially due to an increased haemolysis of the child's blood corpuscles setting in just at that point. Instead, it is probably mainly contingent on lesions to the parenchymatous organs, especially the liver and kidneys, arising while the child is still in the uterus. The fact that a lesion of this kind does not manifest itself until after partus may well be explained by saying that the circulation of the mother had previously dealt, via the placenta, with the waste products from the child's metabolism.

It still seems uncertain whether these parenchyma lesions

arise secondarily to the haemolysis, as a result of it (as is the case in a haemolytic transfusion complication), or whether the Rh antibodies from the mother directly attack not only the blood corpuscles of the child but also, parallel therewith, its other bodily cells. Certain investigations (BOORMAN and DODD 1943) show that the Rh factor is probably not found exclusively in the blood corpuscles, as was originally assumed, but also in other cells of the body. This seems to give reason for assuming that the Rh antibodies may have a direct injurious effect on the other bodily cells also, and not only on the erythrocytes. This now makes it more easy to understand that cases occur where severe lesions to the parenchymatous organs have been observed, despite moderate haemolysis.

### Summary.

The conception that Rh incompatibility between mother and foetus is the cause of familial erythroblastosis foetalis (morbus haemolyticus neonatorum) to far more than 90 % has considerably helped on the diagnosis and prognosis of this complaint. On the other hand, the elucidation of the pathogenesis has meant no material advance in the therapy, apart from the use of Rh-negative blood in transfusions to children with this disease. Judging from his own material, the author considers this improvement of the transfusion therapy to imply only a very modest step forward in the results of our treatment.

Guiding-lines are given for practical experiments to find a protective substance against the haemolytic action of the Rh antibodies in the child's body. It is preliminarily stated that a certain effect of this kind might possibly be ascribed to progesterone. The risk of contracting morbus haemolyticus neonatorum is not decreased for children taken from Rh-immunised women by means of a caesarean section before the onset of labour, not even if this is done several weeks before term.

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FROM THE PEDIATRIC CLINIC OF KAROLINSKA INSTITUTET AT KRON-  
PRINSESSAN LOVISA'S CHILDREN'S HOSPITAL, STOCKHOLM.  
HEAD: PROFESSOR A. LICHTENSTEIN.

## **Experimentally Produced Gallop Rhythm.**

### **A Preliminary Report.**

By

**LARS-ERIK CARLGREN,**

Ever since POTAIN's classic description in 1875 of the gallop rhythm of the heart, many scientists have devoted their attention to this subject. A distinction is made between two main types, viz. a proto-diastolic gallop or the gallop of the third heart-sound, and a prae-systolic gallop or the auricular sound gallop. According to the generally accepted opinion at the present time, these two kinds of gallop sounds are to be regarded as pathologically accentuated third heart-sounds and auricular heart-sounds, respectively. The latter are not infrequently to be found physiologically in children and young people, in particular. While, according to the majority of authors, a gallop rhythm in adults and especially in older people most often indicates a pathologically changed myocardium, in children, on the other hand, at least the third sound gallop is, to a large extent, considered not to be interpretable in this manner, although the question still requires further elucidation.

In the material compiled at the heart station of Kronprinsessan Lovisas Children's Hospital in Stockholm during the last years, several instances of the gallop rhythm occur, the majority being third sound gallops. Some of them obviously concern children with morbid hearts. In most cases, however, particularly serious signs of cardiac injury are lacking. Is the gallop rhythm in these cases of any diagnostic significance? Is it or is it not a sign of myocarditis?



When the staff at the heart station<sup>1</sup> began to turn its attention more closely to these problems, the possibility of producing gallop rhythms by experimental means was discussed. Since, as far as I have been in a position to ascertain, no such investigations have been reported earlier, a preliminary report will be given below of experiments recently performed by me at Kronprinsessan Lovisas Children's Hospital.

A method for producing a myocardial lesion was chosen, which was originally described by FLEISHER and LOEB and has later been employed by several principally American authors. Thus, after having first taken an electro-phonocardiogram, 2.5 cg coffein per kg of body weight were injected intravenously into 41 rabbits, weighing from 2 to 3 kg, and, after 2 to 3 minutes, 0.2 mg adrenalin was added. 11 of the test animals died immediately in connection with the injections. As regards the surviving 30 animals, a series of new electrocardiograms was taken, at intervals varying from 1 day to several weeks. The hearts of most of the animals were subjected to Röntgen examinations, before as well as after the injection, and, as far as possible, simultaneously with the electro-phonocardiograms. One of the animals died after 11 days, probably owing to acute weakness of heart. Another 2 animals died after 10 days and 1 1/2 month, respectively, during experiments with acetylcholin for reducing the heart frequency. The rest were sacrificed after 1 to 2 months by means of a blow on the neck. The hearts were submitted to macro- and microscopic examination. The apparatus described by MANNHEIMER in his work on calibrated phonocardiography was used for the registration of the heart-sounds.

### *Results.*

Among the 30 animals surviving the injection, 20 showed marked changes in the electrocardiogram, consisting mainly of inverted T waves and, to a very small extent, of changes in the S—T segments and splitting of the QRS complexes, while no prolongation of the P—R time was noted. Only 6 animals had, continually, a completely normal electrocardiogram. The changes,

<sup>1</sup> Chief: Dr E. MANNHEIMER.



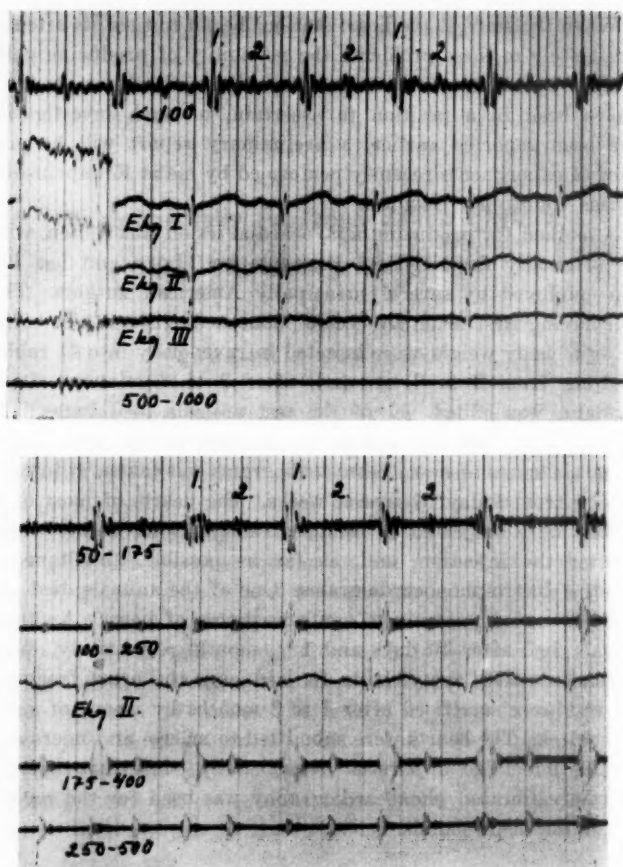


Fig. 1. K 371. ECG and PCG before injection.

which were in good conformity with those described by BECKE, JOHNSON and HARRIS, set in during one of the first fortnights, as a rule on the 4th to the 10th day, disappearing again in some cases after a few days or weeks, while, in others, they remained during the whole observation period which amounted to a maximum of 7 to 8 weeks.

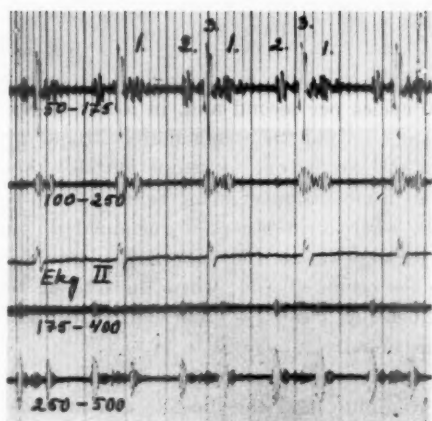
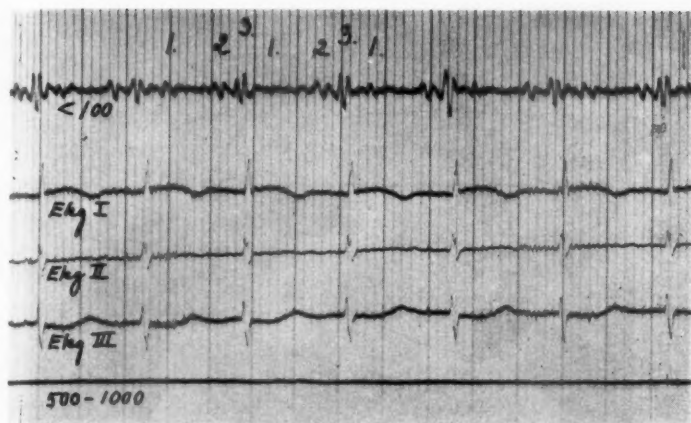


Fig. 2. K 371. ECG and PCG after injection.

In 11 of the animals (about  $\frac{1}{3}$ ), a third heart-sound was perceived on the 4th to the 10th day after the injection, a distance of 0.05 to 0.07 seconds after the beginning of the second heart-sound, being strong enough to justify the term gallop rhythm. It was best registrable within the two lowest frequency ranges, < 100 and 50—175 cycles per second, with an amplitude often

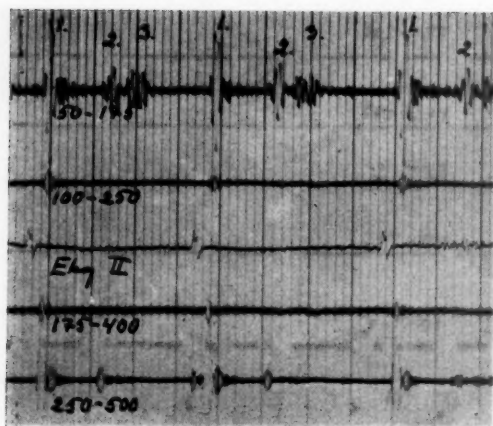


Fig. 3. K 371. PCG at reduced pulse rate by means of pressure on the carotid artery.

exceeding that of the first and second heart-sound, frequently attaining 250 cycles per second and, in a few cases, reaching up to 500 cycles per second. It was generally, though by no means always, constant from one examination to the other and disappeared in some instances after being noticeable for one or several weeks, whereas in others it remained during the whole observation period. In all the cases considerable electrocardiographic changes occurred and, when the size of the heart had been determined by means of Röntgen, often a very marked dilatation was noted.

As the heart frequency of rabbits is very rapid, i. e. 200 to 300 beats per minute, and the diastole consequently very short, the extra sound usually set in after the P wave in the electrocardiogram and close on the subsequent first heart-sound in the phonocardiogram (see Fig. 2). In order to be able to determine whether this was a third sound gallop or an auricular sound gallop, an attempt at reduction of the frequency was necessary. When pharmaceuticals for reducing the rate of the pulse, such as acetylcholin and m-oxi-nor-ephedrin, had been tried without any particular success, this was, in several instances, achieved by

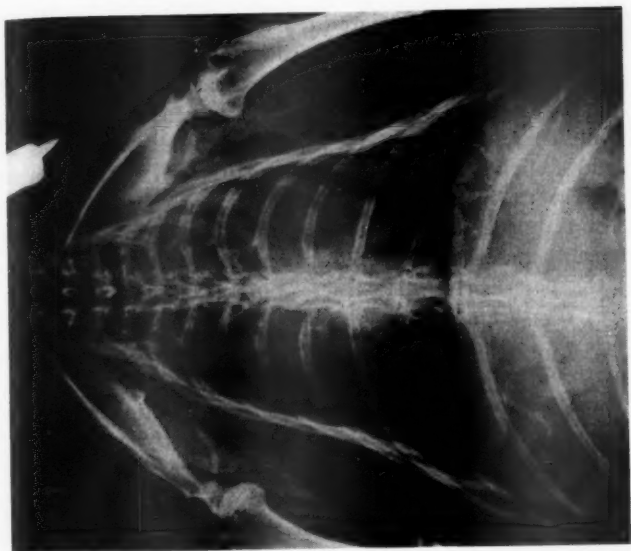


Fig. 4 b. K 371. Heart size after injection.

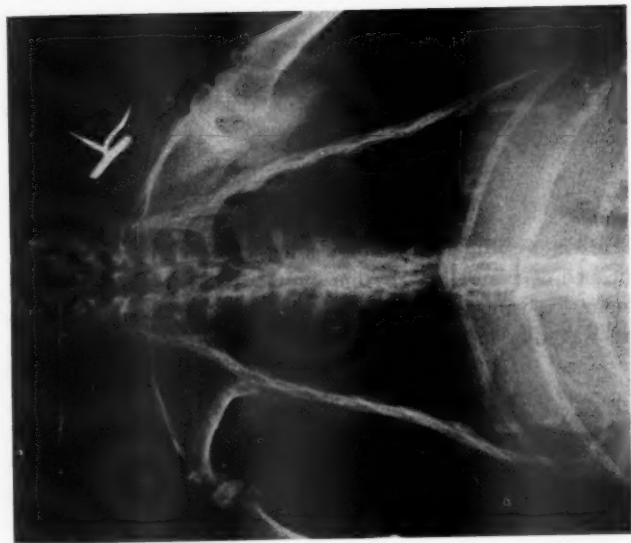


Fig. 4 a. K 371. Heart size before injection.

means of pressure on the carotid artery of one side. It then turned out to be a question of a third sound gallop (see Fig. 3).

In most of the cases, 24 out of 30, the heart was subjected to Röntgen analysis, both before and several times after the injection. Thus, a considerable dilatation was ascertained in 11 cases and a slight one in another 4 (see Fig. 4). It manifested itself on the 4th to the 10th day and remained constant in some of the cases during the whole observation period, while, in others, it diminished though never receding completely.

At the post mortem, the macroscopic examination in many instances revealed a dilatation of the heart which coincided on the whole with the Röntgen findings. In addition, a certain degree of hypertrophy of the dilated as well as non-dilated heart occurred. In a few cases, macroscopically perceptible fibrotic areas were ascertained, invariably being found in the left ventricle and, generally, in the anterior or posterior wall.

The microscopic examination disclosed, in the majority of the cases, more or less extensive fibrosis in the myocardium, sometimes being diffuse, and sometimes more circumscriptive and also, in some instances, a certain degree of lymphocytic infiltration. Both the macro- and microscopic patho-anatomical changes corresponded well with those described by earlier authors.

A more comprehensive account of the experiments will be given later on.

### Summary.

In order to illustrate the question of the appearance and significance of the gallop rhythm and the third sound gallop, in particular, experimental tests were initiated. FLEISHER and LOEB's method was employed for producing myocarditis in rabbits. In about  $\frac{1}{3}$  of the 30 animals surviving an injection, the gallop rhythm was registrable by means of the phonocardiogram. A closer analysis showed, that this was a case of the third sound gallop (i. e. protodiastolic gallop or rapid filling gallop). In all these instances considerable changes were ascertained in the electrocardiogram and often a marked dilatation of the heart. The

patho-anatomical examination, as a rule, revealed a certain degree of hypertrophy and more or less extensive fibrosis in the myocardium.

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FROM THE SURGICAL DEPARTMENT AT KRONPRINSESSAN LOVISA'S  
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## **Megacolon in the Newborn.**

### **A Clinical and Röntgenological Study with Special Regard to the Pathogenesis.**

(A Preliminary Report.)

By

**TH. EHRENPREIS.**

*History.* The introduction of sympathetic surgery in the treatment of megacolon and its rapid progress to a predominating therapeutical position at the present day have again placed in the foreground the so far unsolved problem regarding the pathogenesis of this obscure disease and shed new light on this subject. Since the time of HIRSCHSPRUNG<sup>1</sup>, three different doctrines regarding the question of pathogenesis have prevailed.

1. *Developmental.* HIRSCHSPRUNG<sup>2</sup> interpreted megacolon as a prae-formed anatomical malformation of the colon, analogous to a congenital giant growth of other internal and external organs. This giant colon should not, for mechanical reasons, be capable of emptying in the normal way and would thus give rise to constipation. The malformation theory has derived its principal support from cases where changes have occurred in foetuses<sup>3, 4</sup>, newborns or infants<sup>5-26</sup> which have been interpreted as megacolon. Further, abdominal distension, observed during the first few days of life in cases of megacolon, has been referred to as a sign of congenitally dilated colon<sup>27-29</sup>.

2. *Mechanical.* MARFAN<sup>30</sup>, and others<sup>31-33</sup>, were of the opinion that the patho-anatomical changes were secondary to persistent constipation due to redundancy of the colon and, in particular, the sigmoid. This theory soon predominated over the malformation theory, especially in works by French authors<sup>34-39</sup>.

Also röntgenological transitions from redundant colon to megacolon have, of late, been demonstrated<sup>26, 40, 41</sup>. Kink, valvular and volvulus formations in the sigmoid-rectum<sup>9, 12, 22</sup> have also been described and their appearance attributed to the abnormal length of the sigmoid. However these formations have more and more been regarded as secondary factors and of subordinate significance from a pathogenetic point of view<sup>24, 39, 42</sup>.

3. *Neurogenic*. LENNANDER<sup>43</sup>, BING<sup>44</sup> and HAWKINS<sup>19</sup> considered megacolon to be a manifestation of neuromuscular inertness. FENWICK<sup>45</sup>, WILMS<sup>46</sup>, and others, declared the cause to be a spasm within the sigmoid-rectum part. However, the neurogenic conceptions could not for a long time attract due notice.

On account of the successful treatment of megacolon<sup>47-49, 54</sup> by sympathetic surgery, the study of the pathogenesis acquired new aspects. A correlation between disturbed innervation and megacolon was rendered likely as a result of experimental<sup>50-53</sup>, clinical<sup>54</sup> and pharmaco-dynamic<sup>55-58</sup> investigations. Nevertheless, the support of the neurogenic theory, so far offered, does not serve as definite proof. The efficacy of interventions on the sympathetic nervous system does not prove the nature of the operation as a causal therapy<sup>49, 52</sup>, but merely confirms the accuracy of our conceptions regarding the innervation and physiology of the colon. Elimination of the sympathetic influence should improve bowel function, even in the presence of a congenital dilatation of the colon or a relative obstruction, whereas elimination of the parasympathetic influence should counteract this activity. This has, in fact, been proved experimentally. Thus, division of the parasympathetic nerves to the distal colon in animals produced constipation and bowel dilation<sup>50-52</sup>. FONTAINE and BÉRARD<sup>53</sup> found that the symptoms which then appeared were only temporary and left no patho-anatomical changes. These investigations, as well as the appearance of megacolon after prolonged atropine medication<sup>56</sup>, merely indicate that the disease may occur owing to inhibition of the parasympathetic innervation.

*Introduction to problem.* The megacolon disease may be defined clinically as a severe disturbance to bowel function and,



anatomically, as dilatation and hypertrophy of the colon, or part of it, in the absence of a manifest cause. However, redundancy of the colon and the sigmoid, in particular, has been advocated as a potential cause. The primary and, as yet, unsolved problem concerns the connection between disturbed function, dilated colon and redundant colon. Each one of these factors may be the primary one from an etiological point of view, these three possibilities being represented by the three pathogenetic theories mentioned above. The possibility of morphological-mechanical causes having been established, the disturbed bowel function may be denoted as primary, only provided these causative factors are excluded. Past clinical studies of megacolon are based almost entirely on materials comprising older children and adults. In those cases it is very difficult to distinguish between primary and secondary changes. This will, no doubt, explain why such a fundamental problem as the one propounded above has not yet been definitely solved. Isolated cases have earlier been observed in newborns<sup>3-26</sup> and have been interpreted as support of the malformation theory.

*Material.* In the course of a few years of studies of different ileus conditions in newborns<sup>59, 60</sup>, I have come across 5 megacolon cases which began at birth and were submitted to clinical and röntgenological examination during the first 10 days of life. In a perusal of the whole megacolon material at the Kronprinsessan Lovisas Children's Hospital since 1906 when the first case was registered (65 cases), another 4 were found, i.e. 9 cases in all. 8 of the children were boys.

For the sake of comparison, the colon of 100 healthy children of both sexes has been examined after barium enemas during the first 10 days of life.

*Onset. Clinical.* The 3 cardinal symptoms were constipation, abdominal distension and vomiting. 2 cases began with diarrhoea which changed over to constipation after 4 and 6 weeks, respectively. The distribution of the symptoms and the time of their onset will be seen in the table. The figures denote the day of life on which the several symptoms appeared (observed in all cases at the maternity department where the child was born).

Case No. . . .	I	II	III	IV	V	VI	VII	VIII	IX
Constipation . .	1	1	1	1	1	1	1	-	-
Distension . . .	3	3	4	2	3	-	5	2-3	2
Vomiting . . .	3	-	2	-	3	1	5	2-3	2

Thus, the clinical picture of the onset in all the cases more or less resembled that of intestinal obstruction.

*Röntgenological.* An abdominal survey disclosed increased gas content restricted to the colon in 4 cases and comprising the small intestine in another 4 (Fig. 1 a). (In the ninth case the survey picture is missing.)

The width, length, excitability and emptying ability of the colon has been studied in close relation to the same conditions in normal newborns (Figs. 2-7).

The width of the colon does not show any gross deviation from the normal size in 6 of the cases (Figs. 2-4 ×). In 3 cases (Figs. 5 × and 10 ×) the colon is somewhat wider than normally.

The length of the colon varies within normal limits (Figs. 2-5).

The excitability and emptying ability of the colon is greatly reduced in all the cases.

The colon in healthy newborns is extremely excitable and reacts very strongly to the injection of contrast enema<sup>37, 61, 62</sup>. The pressure produced by the routine elevation of the enema jar 70 cm above the level of the table, is too strong in the case of healthy newborns and elicits marked contractions and instantaneous emptying of the enema. When the jar is lowered to 50 cm or below, the examination is still unsuccessful in some cases. As regards the megacolon, such precautions were not required, and the colon filled fairly well in all the cases. The difference is evident also from the aspect of the filling pictures (Figs. 2-5). The normal cases have more haustrations and the impression of life obtained by them is quite another than that given by the megacolon pictures. The emptying takes place almost immediately and is practically complete in healthy newborns (Fig. 6), whereas it has nearly ceased in the megacolon cases (Fig. 7).

*Course.* In 8 cases the constipation became persistent. When not promptly relieved by enemas, renewed abdominal distension and vomiting fits ensued. In the ninth case the symptoms have been and still, at the present age of 1 year, are periodical with

long intervals of apparent health. 4 of the children died of their megacolon disease at  $2\frac{1}{2}$ , 3, 15 months and 9 years, respectively, while the remaining 5 are alive and, at present 1—15 years old.

Röntgenologically the megacolon picture appeared within a time which could be determined in 3 instances as from 3 to 6 weeks (Fig. 8). The case with intermittent symptoms still at the age of 1 month revealed a normal colon picture (not reproduced), and at  $3\frac{1}{2}$  months only a moderate dilatation of the sigmoid (Fig. 9) which, at the age of 10 months, had developed into a colossal dilatation of the whole colon (not reproduced). In the remaining 5 cases (Figs. 9—10) the interval between the first and second X-ray examination is longer and gives no idea of the time of development. In some cases the colon was fairly redundant at the first X-ray examination, whereas this redundancy disappeared at the development of megacolon. (Figs. 8—9.)

*Discussion.* When the megacolon disease has reached the point of clinical as well as röntgenological manifestation, there is no longer any possibility of determining the primary pathogenetic factor. However, a distinct differentiation occurs in the degree of development before the changes have deteriorated that far. At the onset, this difference is so marked as hardly to leave any room for doubt regarding the primary process.

The disturbed evacuation was at its maximum from the onset in all the cases. The dilatation had hardly begun at the first examination in 6 cases and was but slight in 3. Thus, the disturbed emptying cannot be explained as due to a congenital colon dilatation.

The slight dilatation in 3 of the cases can be fully accounted for without the occurrence of developmental errors.

Firstly, these cases represent a more or less marked ileus condition. The gas filling, which in one of the dilated cases (Fig. 10 x) distinctly outlines the colon, may also cause its distension. The significance of this factor is evident from another case (Fig. 1 b). On the fifth day of life, this case disclosed a dilated colon filled with gas. The ileus condition was relieved after intestinal rinsing and, on the eleventh day of life, an abdominal survey showed a normal gas filling and the contrast enema a colon of normal width.

Secondly, the reduced excitability of the colon renders possible a certain degree of artificial distension by the pressure of the enema. On the other hand, in normal newborns the colon is so excitable as to preclude all possibility of distension by means of the technique employed, even when attempts are made to increase the pressure.

Thirdly, the children are, of course, young at the first examination but not quite newly born. Thus, an indicated or beginning colon dilatation has had a chance to develop, considering the comparatively rapid progress of the changes (Fig. 8).

The redundancy of the colon is obviously congenital but is not more pronounced in megacolon cases than in normal ones (Figs. 2—5). Accordingly, it cannot, reasonably, be supposed to possess pathogenetic significance. Nor was any localized obstruction detectable, whether clinically or röntgenologically, which also applies to 4 post mortems and 2 laparotomies.

*Thus, the disturbed evacuation cannot be explained by morphological-mechanical factors and should, therefore, be denoted as primary, neurogenic or purely functional.*

These findings contrast with earlier observations regarding megacolon in fetuses and infants. A survey of the published cases under the age of 1 month <sup>3—26</sup> discloses that none can be denoted as definite proof of the malformation theory. The younger cases <sup>3—17</sup> concern chiefly patho-anatomical findings of such an unspecific or atypical kind as to render the megacolon diagnosis indefinite, the remaining cases <sup>18—26</sup> being, at the time of observation, too old to offer any evidence of the congenital nature of the disease. Nor do cases with abdominal distension soon after birth <sup>27—29</sup> indicate the occurrence of a congenital dilatation of the colon. The distension of the abdomen is, in the case of megacolon in newborns, a manifestation of a disease picture resembling ileus (Fig. 1 a) and not, as in older children, of colonic dilatation.

The importance attached to the redundancy of the colon is probably due to insufficient knowledge of the normal anatomy of the colon in newborns. It has only lately become evident from some röntgenological works <sup>37, 61—63</sup> that the colon in newborns and infants practically always reveals marked redundancy and that no connection exists between the degree of this redundancy and the motor function of the colon <sup>62—64</sup>. No doubt, the redundancy of the colon in newborns and infants is also from a genetic point of view different from that of adults. Measurements which have been carried out <sup>65—68</sup> show that the length of the colon, in relation to that of the body or trunk, is greater in newborns than

in adults. However, the difference is insignificant, when calculated to approximately 5 cm. Thus, the redundancy of the colon in newborns can only to a very small extent be explained by an actual increase in the length of the colon. The sinuous course is probably due chiefly to the fact that the space left to the colon in newborns is considerably reduced by the large liver, on the one hand, and the narrow pelvis, on the other. When the child grows, the relative size of the liver decreases and the pelvic volume is increased, whereupon the colon can unfold its many loops and assume its definite shape. In view of this, it becomes natural that the frequency of redundant colon in newborns should be almost 100 per cent. This redundancy should be regarded as a physiological occurrence characteristic of that age and lacking patho-genetic significance.

Thus, transitions between a redundant colon and megacolon <sup>26, 40, 41</sup> actually disclose the same course as the above-mentioned cases, viz. that the colon is röntgenologically of normal length and width from the beginning and only becomes dilated secondarily.

The significance of a real obstruction is obvious with regard to the appearance of megacolon. Interventions on account of anal atresia often result in a fibrous stricture of the anal opening with severe constipation and secondary dilatation of the bowel. These cases are referred to as secondary or symptomatic megacolon. Clinically, röntgenologically and patho-anatomically, they resemble the idiopathic megacolon, but clearly differ owing to the existence of a manifest cause which does not necessarily have to be mechanical. Megacolon may occur after injuries and diseases affecting the autonomic nervous system <sup>54</sup>, either centrally or peripherally, at endocrine disturbances <sup>54</sup> (myxedema, acromegaly), and after prolonged atropine medication <sup>54</sup>. As will be seen from the introduction the purpose of the present paper is to study the idiopathic form. The non-existence of a localized obstruction is, in these cases, inherent in the nature of the term itself.

Attempts to establish the particular kind and etiology of the disturbed function which forms the basic factor in the development of megacolon, have, so far, not given any definite results. Investigations referred to in the history <sup>47-58</sup> have rendered it likely that the autonomic nervous system plays a part in the pathogenesis. So far it is difficult to decide whether changes in the vegetative nervous system itself constitute the innermost cause of the disease, or whether its cooperation is limited to the transmission of pathological impulses from a superior (endocrine?) centre.

Microscopical changes in Auerbach's plexus <sup>69, 70</sup> or sympathetic ganglions <sup>71, 72</sup> have been described. Nevertheless, other investigators <sup>11, 55, 73</sup> have called their existence in question.

As regards the mode of origin of the disease, an interesting hypothesis has been suggested by ASK-UPMARK <sup>24</sup> and further elaborated by PÄSSLER <sup>54</sup>. It is based on a combination of two known conditions, viz. 1) that meconium is not evacuated during foetal life and 2) that the paraganglion aorticolumbale, during foetal life and, in particular, towards its termination, develops considerably, only to disappear gradually after birth. PÄSSLER assumes a physiological meconium retention in the foetus owing to sympathetic influence from the ganglion aorticolumbale on the sphincter ani, and that abnormal persistence on the part of this mechanism should result in megacolon.

As long as the disturbance to the evacuation lacks a definite neuro-anatomical substratum, the term neurogenic seems to transcend the limits of our knowledge of the pathogenesis. Our attitude towards the continued penetration of this problem in this way might be enclosed within too narrow boundaries. It is, no doubt, most consistent with our prevailing terminology and present state of knowledge to define, for the time being, the disturbed evacuation as a functional disorder.

Two other diseases occur in the digestive canal which in certain ways resemble megacolon, viz. pylorostenosis and intussusception. These three diseases have in common a predominance of small children of the male sex. Thus, approximately 80 per cent of the cases at the Kronprinsessan Lovisas Children's Hospital of megacolon <sup>73</sup>, pylorostenosis <sup>74</sup> and intussusception <sup>75</sup> were boys and similar figures may be found in other published materials. They cannot be interpreted as incidental. Nor can the appearance of the above-mentioned diseases be promoted by known anatomical differences between the sexes. Therefore, it seems probable that the male predominance has particular significance with regard to the etiology.

The probability of a mutual factor in the genesis of megacolon and pylorostenosis has been propounded earlier on a theoretical basis <sup>75-77</sup>. WALLGREN <sup>78</sup> has recently been able to prove that pylorostenosis is not due to a prae-formed, röntgenologically detectable hypertrophy or stenosis of the canalis ventriculi.

WALLGREN examined the stomachs of 1000 newly born boys after contrast meal. On the basis of earlier investigations, he calculated that 6 of these children would fall ill with pylorostenosis. He did, in fact, subsequently succeed in finding 5 cases among the 1000 with manifest pylorostenosis and typical X-ray changes. None of them had shown any changes at the first prae-clinical X-ray examination.

The study of megacolon cases in newborns described above has produced a similar result as regards megacolon. Attempts to establish a pathogenetic correlation between the megacolon and pylorostenosis have in this way been given a factual basis, suggesting that a continued study along uniform lines might contribute towards a final solution of the question of the pathogenesis of these two diseases which have for so long been a bone of contention.

### Summary.

1. A clinical and röntgenological study of the onset and course in 9 megacolon cases in newborns discloses that the primary genetic factor in the etiology of the disease is a disturbance to the emptying of the bowel.
2. The röntgenological megacolon picture is a secondary development to this disturbance, occurring within a varying period of time, which was established in 4 of the cases to be from 3 weeks to 3 1/2 months, while it may be longer or shorter in other cases.
3. Redundancy of the colon and, in particular, the sigmoid was not more marked than in normal newborns. Nor was any other obstruction ascertainable.
4. The study of these megacolon cases in comparison with normal newborns has revealed the untenability of the arguments which have supported the malformation and obstruction theories:
  - a) The cases earlier described as megacolon in newborns and infants are either too old to prove the congenital nature of the changes, or too uncertain to reveal their megacolon nature. The abdominal distension soon after birth in cases of megacolon is a manifestation of a disease picture resembling ileus and does not prove the congenital dilatation of the colon.



- b) The significance attributed to colonic redundancy is based on insufficient knowledge of the normal anatomy of the colon in newborns. The redundant colon in newborns can only to a very slight extent be explained by an actual increase in the length of the colon. It is, no doubt, chiefly due to the fact that the space left to the colon is considerably reduced in newborns by the largeness of the liver and the smallness of the pelvis. This gives rise to a sinuous course of the colon which is the rule in normal newborns and must be considered as physiological with regard to that particular age.
5. Thus, megacolon may be characterized as a dilatation and hypertrophy of the colon owing to disturbed evacuation of the bowels. The particular kind of disturbance and the possible existence of a neuro-anatomical substratum have not as yet been elucidated. It is therefore consistent with prevailing terminology to define, for the time being, this disturbance as a functional disorder.

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Fig. 1 a. Abdominal survey (case of megacolon).

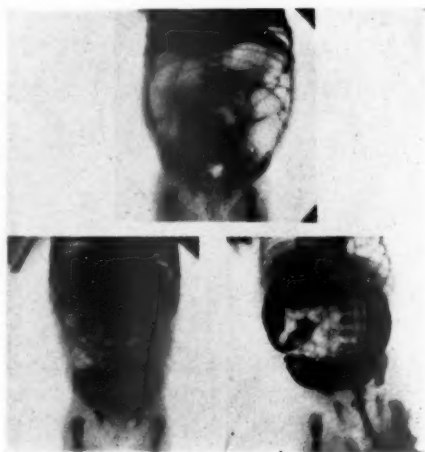
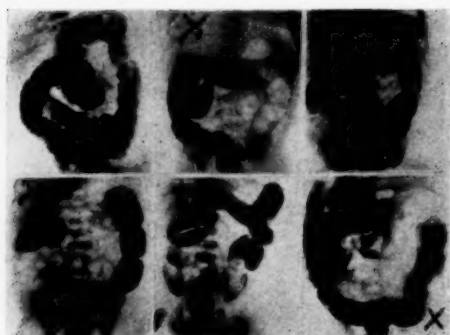
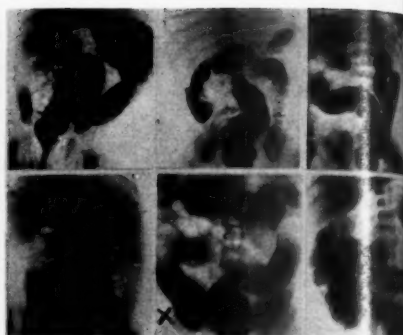


Fig. 1 b. Significance of gas distension of colon.

Upper row: abdominal survey on the fifth day of life in one case of megacolon.  
 Lower row: abdominal survey and contrast enema on 11th day of life in the same case.



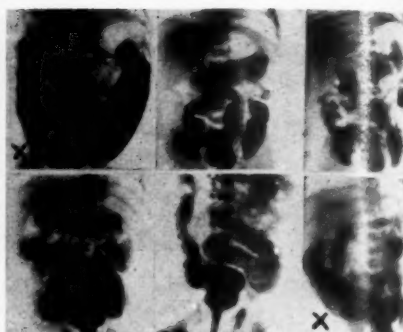
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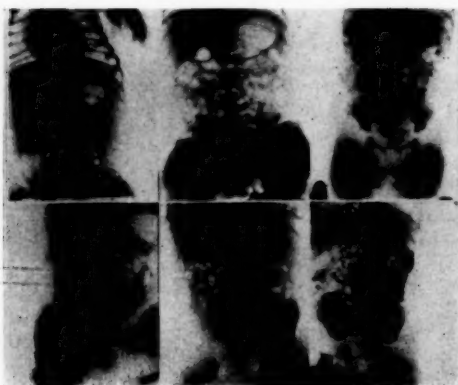
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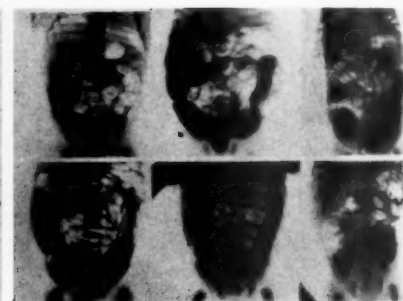
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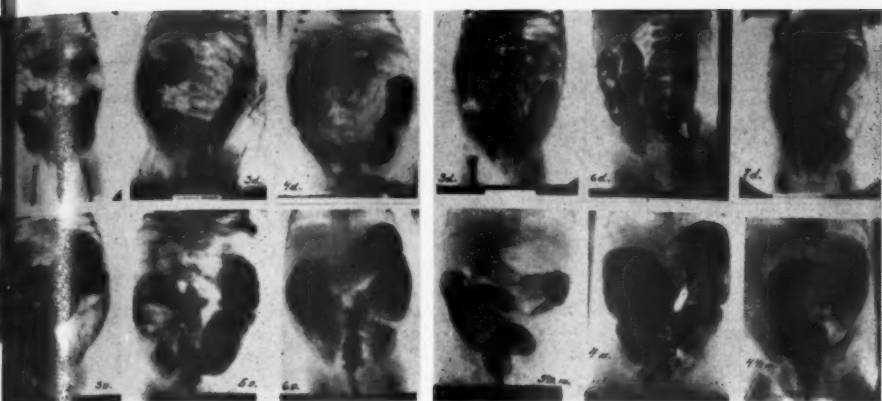
Figgs. 2—5. Röntgenograms of colons after barium enema in megacolon cases (x) and normal newborns.

Fig. 6. Immediate emptying of contrast enema in 6 normal newborns.

Fig. 7. Emptying of contrast enema in 4 cases of megacolon in newborns.

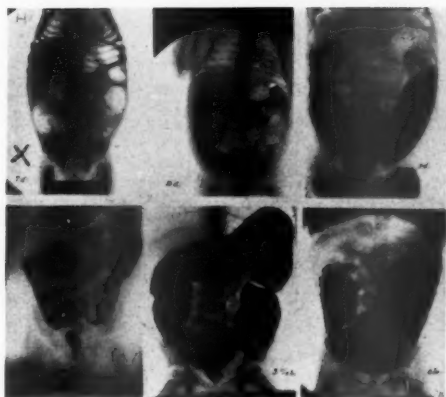
Upper row: immediate emptying in 3 cases.

Lower row: immed. empt., 24 h.-empt. and 48 h.-empt. in one case.



8

9



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Fig. 8—10. Röntgenological development of megacolon.

Upper row: first X-ray examination in 9 cases of megacolon in newborns.

Lower row: first X-ray examination with röntgenological megacolon in the same cases.

Abbrev.: d. = day, v. = week, m. = month, år = year.



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FROM THE SAMARITEN CHILDREN'S HOSPITAL, STOCKHOLM.  
HEAD: N. MALMBERG, M. D.

## **Treatment of Pyloric Stenosis in Infants with Methylscopolamine Nitrate.**

By

**OLLE ELGENMARK.**

The treatment of pyloric stenosis has for many years been carried out according to a definitely fixed plan. The first measures are conservative, and then, if these fail to produce the desired effect, a surgical intervention is undertaken. As conservative treatment, the practice is to place the child in peaceful surroundings by arranging for the necessary isolation, and to secure adequate nutrition. In many instances these measures are sufficient. In others, improvement does not occur until after the institution of medicinal treatment, usually in the form of an antispasmodic. Atropine, in doses to the point of intoxication, is the substance generally used, but during the past few years eumydrine (atropine methylnitrate) has won much favour owing to the fact that its toxicity is much lower than that of atropine while at the same time its therapeutic effect is much greater.

Conservative treatment of pyloric stenosis, however, does not always have the desired effect. In some infants the vomiting continues with undiminished intensity, and in these the only hope of achieving an improvement in the condition lies in an operation. The frequency with which surgery is used for this complaint varies in different countries and at different hospitals, depending partly on the resources available to cope with the trying and time-consuming conservative treatment, and also on the experience and the attitude to the operative possibilities of the physician in charge of the case. At some hospitals operations are performed at an



early stage, at others not until every likely form of conservative treatment has been tried. Consequently, in some hospitals, up to two-thirds of all the cases are operated upon, while at others the corresponding figure is very low. At the Samariten Hospital for Children's Diseases, operation has been undertaken in 23 percent of the material from the past ten years. The practice at this hospital has been to operate if the conservative treatment has not produced a permanent result within one week. There is no contra-indication to the operation apart from an extremely bad general condition. For the operation to succeed, however, it is necessary that the surgeon should have had special training. In countries where this intervention is performed by operators without special training the mortality consequent upon operation is high.

Since the summer of 1944, a new drug has been in use at this hospital for the non-operative treatment of pyloric stenosis. In 1942, E. NYMAN introduced methylscopolamine nitrate as a first-class antispasmodic having no toxic by-effects. The compound is manufactured by A. B. Pharmacia, Stockholm under the name of »Skopyl». It is sold in tablets containing 0.0005 g of methylscopolamine nitrate, and it has recently been made available as a solution with the same concentration to one milliliter. According to a recent investigation (LOMBOLT, 1944) scopolamine has 8 times as strong an effect when administered subcutaneously than when given by mouth. The experiences gained with Skopyl point in the same direction (NYMAN, 1944).

An agent with such a strong antispasmodic action and such slight toxicity was thought to be worth trying out in pediatric practice, despite the fact that scopolamine has always been regarded as being poisonous to children, and infantile pyloric stenosis seemed a suitable complaint upon which to study its effect.

The material described in this paper is composed of 9 infants with roentgenographically confirmed pyloric stenosis. Six of them lost all symptoms within one or a few days — the vomiting ceased or was reduced to a minimum, the restlessness disappeared and the infant began to put on weight. In 3 of them conservative treatment brought no relief and they were operated upon by the

Rammstedt method. The course of the illness in these patients was so interesting that a more detailed report seems worth placing on record.

### Case Reports.

*Case 1.* A girl, aged 5 weeks, who was admitted to the hospital at the age of 3 weeks because of attacks of cyanosis and signs of congenital vitium cordis. After 14 days in hospital projectile vomiting

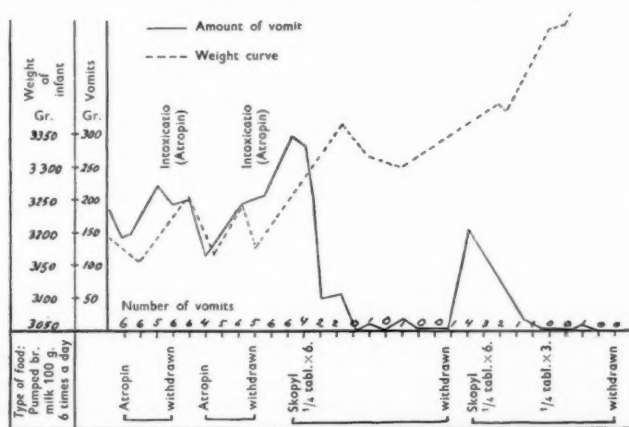


Fig. 1.

started. Waves of contraction were distinctly visible in the epigastrium, and she began to lose weight. Roentgen examination revealed a strictured pyloric canal and greatly delayed evacuation of the stomach. The accompanying diagram (fig. 1) shows the course from the time when the stenosis was diagnosed.

As may be seen from the diagram, the patient showed signs of atropine poisoning on two succeeding occasions after medication. The vomiting continued and her general condition deteriorated. Skopyl had an instantaneous effect. The vomiting ceased almost entirely and her general health improved. Ten days later the administration of Skopyl was tentatively discontinued, but the result was an immediate deterioration. A second course of Skopyl caused the symptoms to disappear again. Since then she has been symptom-free despite the fact that the Skopyl was withdrawn again at the end of 9 days.

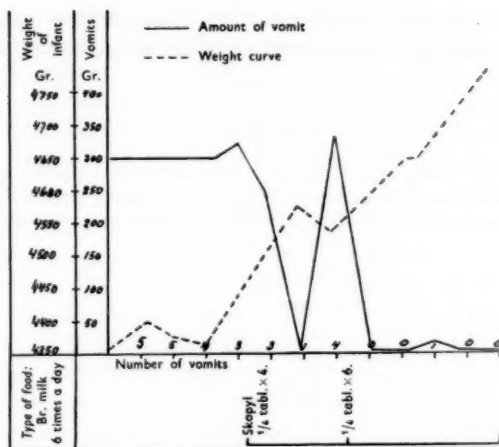


Fig. 2.

*Case 2.* A boy, aged 2 months, who had been vomiting profusely since the age of 3 weeks. Atropine sulfate in tablet form was prescribed but the child showed no improvement. The mother, who was a trained hospital nurse, suspected pyloric stenosis and made repeated attempts to stop the vomiting with atropine in various doses, but without success. The total daily amount of vomit was estimated at between 300 and 400 g. As he was losing weight at an alarming rate and his general health was deteriorating, a children's doctor was consulted and the child was then sent to this hospital for treatment. On admission the physical examination disclosed a much emaciated child with a pained expression and suffering from periodic attacks of restlessness. He had projectile vomiting attacks after his meals. In the epigastrium there were noticeable waves of contraction. Roentgen examination verified the diagnosis of pyloric stenosis. Skopyl treatment was instituted and the vomiting ceased when the dose was increased from a  $\frac{1}{4}$  tablet 4 times a day to a  $\frac{1}{4}$  tablet 6 times a day, taken half an hour before meals. After 11 days' treatment the patient was discharged as cured, and a fortnight later the report was received that he was still well despite the fact that the Skopyl tablets had been stopped a week before.

*Case 3.* A girl, aged 3 weeks, who had been suffering from projectile vomiting for a week. On her admission, powerful peristaltic movements in the stomach were established and a roentgenogram revealed the presence of stenosis of the pyloric canal.

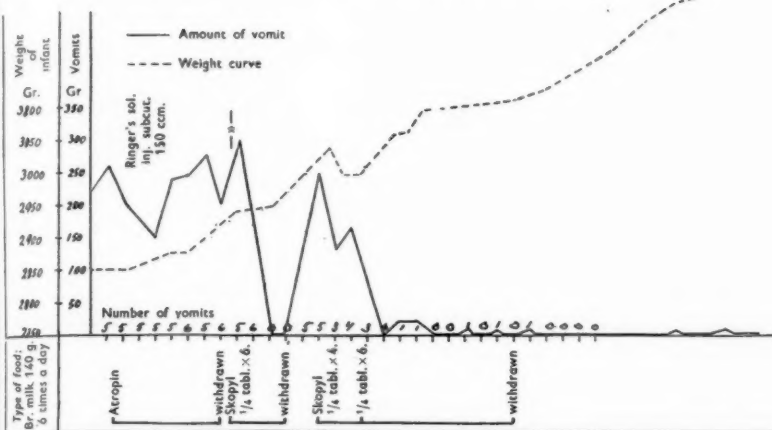


Fig. 3.

As may be seen from figure 3, there was no improvement from a 7 days' course of atropine. The patient's general condition was deteriorating. A small dose of Skopyl had little effect, but a »full dose» (a  $\frac{1}{4}$  tablet 6 times a day half an hour before meals) stopped the vomiting immediately. As an experiment, the treatment was withdrawn at the end of one day and 2 days later the amount of vomited matter was the same as before. Skopyl (a  $\frac{1}{4}$  tablet before each meal) again resulted in cessation of the vomiting, and since then the patient has only had about one small vomiting attack each day.

*Case 4.* A boy, aged 5 weeks, who had been vomiting copiously for a week. The stomachal peristalsis was plainly visible, and stenosis of the pylorus was established by roentgenography. After a 5 day's observation period, during which the patient threw up large quantities after every meal, Skopyl treatment (a  $\frac{1}{4}$  tablet 6 times a day) was started and the vomiting ceased immediately. At the end of 8 days the treatment was discontinued and 10 days later he was discharged as cured.

*Case 5.* A boy, aged 6 weeks, who had been suffering from projectile vomiting for a week and had lost weight alarmingly. When admitted to the hospital he was much emaciated. Peristaltic waves of contraction were plainly to be seen in the epigastrium. Roentgen examination showed that the pyloric portion of the stomach was constricted. After 2 days' observation, during which the patient vomited copiously, Skopyl (a  $\frac{1}{4}$  tablet 6 times a day before meals) was administered. The immediate

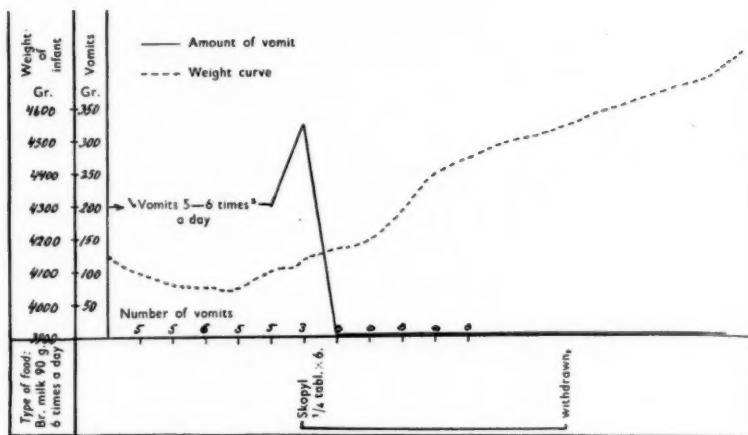


Fig. 4.

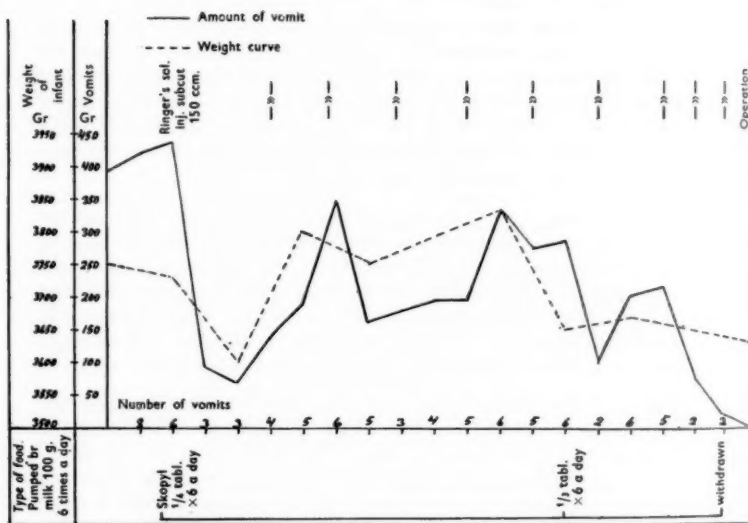


Fig. 5.

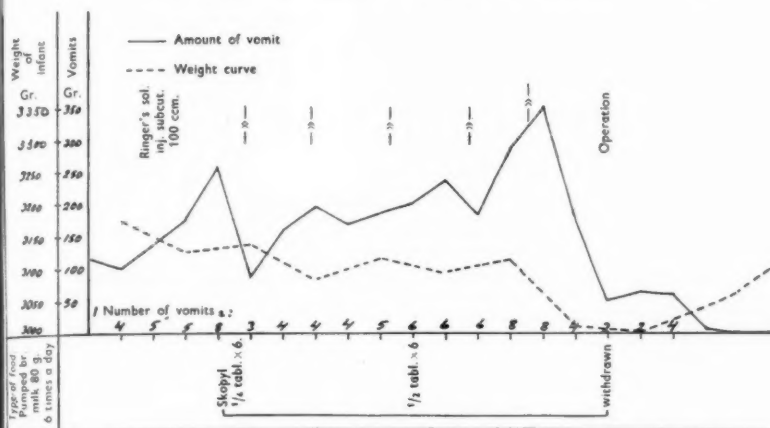


Fig. 6.

result was a decrease in the amount of vomit from 400 to 100 g per day, but the vomiting did not cease. After 18 days' treatment with Skopyl without satisfactory improvement, the Rammstedt operation was performed after which the vomiting ceased at once.

*Case 6.* A girl, aged 3 weeks, who had had projectile vomiting attacks for 4 days. On admission to the hospital manifest contractions of the stomach were observed, and there was roentgenologic evidence of pyloric stenosis. During an observation time of 4 days she had up to 8 attacks of vomiting each day. Skopyl given before meals brought no relief, not even when the dose was increased after 5 days from quarter to one-third of a tablet 6 times a day before meals. At the end of another 5 days an operation was performed. She was then sent home, free from all symptoms. Eight days later she was admitted again suffering from projectile vomiting. Waves of contraction were plainly evident in the epigastrium. Skopyl (a  $\frac{1}{4}$  tablet 6 times a day) now had an instantaneous effect, and there was no return of the vomiting after the withdrawal of the treatment 6 days afterwards.

*Case 7.* A boy, aged 7 weeks, with projectile vomiting of 8 days' standing. Roentgen examination disclosed a stricture of the pyloric canal 2 cm in length. During 4 days' observation he had projectile vomiting attacks after every meal. Skopyl put an immediate stop to the vomiting. He was discharged after 14 days in hospital and has had no return of the complaint.



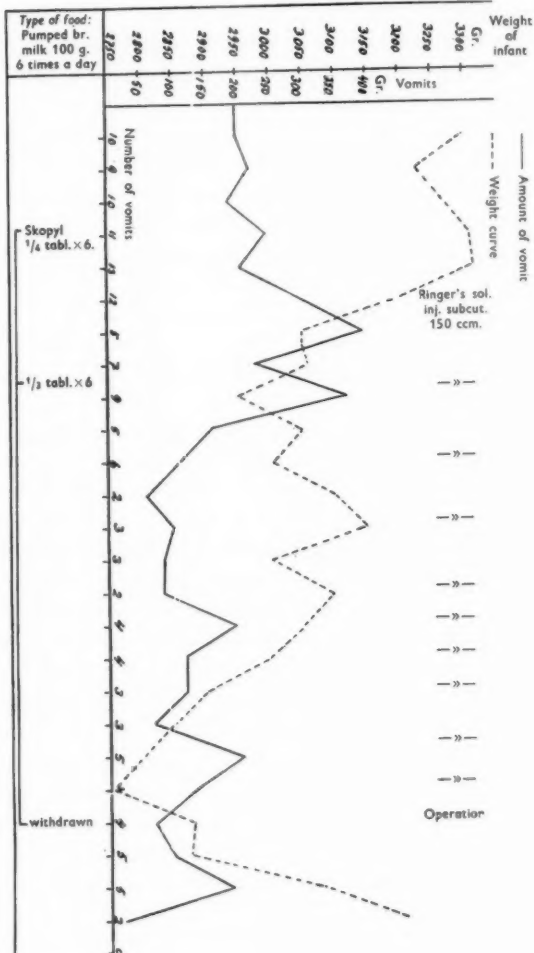


Fig. 6.

like atropine and eumydrine, has its limitations, for reasons at present unknown, and it is to be wondered, therefore, whether methylscopolamine nitrate really does possess advantages over other well-tried agents which have been in use for many years.



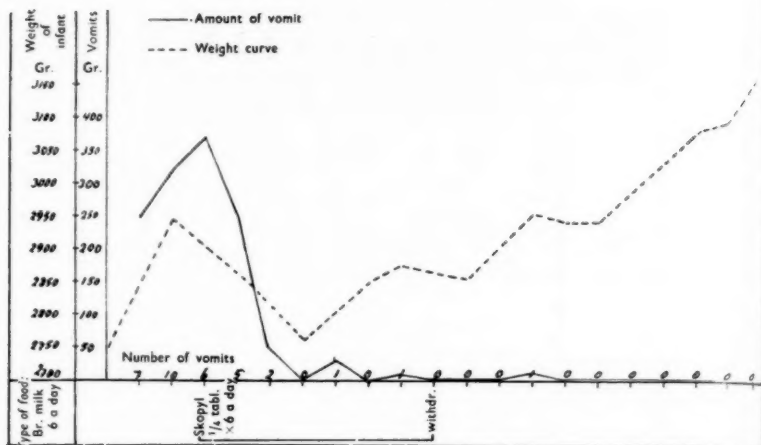


Fig. 9.

One objection to atropine therapy is that the risk of intoxication is far from slight and that deaths have been known to occur when it has been applied. Further, an idiosyncrasy to atropine, making atropine treatment impossible, is present in some patients. Cases 1 and 3 are good illustrations of occasions when atropine could not be used. Eumydrine, on the other hand, seems to be fairly harmless, although some authors state that unaccountable deaths have been due to eumydrine poisoning.

The advantage of methylscopolamine nitrate would seem to be that its potency as a vegetative antispasmodic is several times greater than that of atropine and eumydrine, a quality reflected in the *rapid effect* which produces instantaneous stagnation in the vomiting in cases responsive to antispasmodics. That this spasmolytic effect is not one exercised on the hypertrophic muscles in the pyloric canal has already been demonstrated by other investigators, because the muscular hypertrophy proved by roentgenography persists for several years after all symptoms have disappeared. Nor are the peristaltic movements of the stomach affected by either atropine or scopolamine in anything but very large doses. The only other explanation is a spasmolytic effect

on the mucous coat of the canal. In the cases resistant to conservative treatment it is possible that the mucous membrane in the pyloric canal is so rich in folds that passage out into the duodenum is hindered even though the mucous coat does not cause obstacles through its contraction. In certain cases it is possible also that an edematous condition of the mucous membrane may be a contributory cause of pyloric stenosis.

In addition to this superior spasmolytic effect, methylscopolamine nitrate possesses another advantage over the other previously-mentioned drugs, an advantage which is of great importance in pediatric practice, and that is its slight toxicity. Skopyl has been found to have no deleterious effects whatsoever, even when it has been administered over long periods. In isolated cases, a transient flush is observed, but there are no accompanying signs of poisoning and no change in the medication has been necessary in these patients. On account of its almost complete lack of toxicity Skopyl can be used to advantage for ambulant patients.

Skopyl has also been found effective in the treatment of other forms of infantile vomiting such as habitual vomiting, and it has been put to wide use for these conditions at this hospital. Even very small and debilitated infants tolerate Skopyl well. For this type of vomiting the dose has varied, a  $\frac{1}{4}$  tablet being given 3 times a day in some cases and a  $\frac{1}{4}$  tablet 5 times a day in others, according to the age of the patient and the severity of the vomiting attacks.

The great value of methylscopolamine nitrate in internal medicine has been demonstrated in several publications by E. NYMAN, and it has been shown to be a sure and superior antispasmodic in cases where other agents have proved ineffective. This drug may in the future prove to be of the same value in pediatric practice, for children suffering from convulsive states such as spasmophilia and toxic spasms, where a sure and rapid effect is desirable. In any case, methylscopolamine nitrate has proved to be an excellent and safe antispasmodic, far superior to the previously used drugs, for infantile pyloric stenosis and other forms of vomiting common to children.

### Summary.

Methylscopolamine nitrate has proved to be a superior antispasmodic in internal medicine, and it therefore seemed likely that it might be equally valuable in pediatric practice, in particular in the treatment of infantile pyloric stenosis. In 6 of the 9 patients treated immediate cessation of the vomiting, improvement in the general condition, and a gain in weight was achieved. Three patients did not respond to the treatment and an operation was necessary. The most striking feature was the rapidity with which the effect occurred. In many of the infants it occurred on the same day as the first dose, and in any case an improvement was noted within a few days. Another quality of this drug which makes it especially suitable for use in children is its harmlessness. Not even after a long period of medication were any by-effects to be observed, other than a sudden flush which rapidly subsided.

The drug has also been tried and proved to be very effective in the treatment of other forms of vomiting occurring in infancy.

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## **The Reaction of First-Born Children in Infectious Diseases.**

By

**NILS FAXÉN.**

In a previous article (*Acta Pæd.* 26, 1939) the author has tried to show that first-born children react with longer periods of temperature in scarlet fever than later-born children. Some sources of errors were pointed out which must be taken into consideration in the elaboration of the material. The method applied in the above article is not completely satisfactory, however, for which reason I have desired to submit an examination where the said sources of errors are eliminated with greater security. Material as well as questions have been increased as will appear from the following.

The material used for the first part of this article consists of all cases of scarlatina in the ages 0—12 years nursed in the Hospital for Infectious Diseases in Gothenburg during a period from 1917—1938, in all 6 000 cases approximately. During this time all cases of the disease known in this town were treated in the said hospital, for which reason a sifting of the material before admission to the hospital may be completely ignored.

The study of initial fever in scarlatina has been based on temperatures measured in hospital during the first ten days of illness which period has been arbitrarily chosen as the initial stage. Thus the anamnestic statements concerning temperatures have not been taken into consideration, nor has any attempt been made at estimating the temperature-curve before the hospital treatment. The number of children observed on each day of the disease has been recorded as well as the number of those who on that day showed a temperature of 38° C or more. In this way the source of the error due to the fact that children belonging to a certain group may have been admitted to hospital treatment at an earlier

phase of the disease than others is avoided. As soon as any patient showed signs of complications such case was excluded from the material from and on that day. Lymphadenites on the neck appearing during that period have, however, not been considered as a complication.

The children have been divided into five groups: 1) Single children, 2) First children with short intervals till nearest younger children (1—5 years), 3) First children with long intervals to next children (exceed. five years), 4) Laterborn children with short intervals till nearest elder children (1—7 years), 5) Laterborn children with long intervals, »latecomers» (over 7 years).

In so far as no other source has been given the statistical methods have been taken from Bonnier-Tedin: *Biologisk Variationsanalys*. The original tables are to be found in a Swedish version of this paper appearing in *Hygien* (Nordisk Medicin). Here only the end results of each computation are presented.

As regards the above stated groups 1, 2 and 4 the elaboration is made on the percentage-figures of febrile children within each age-group on the sec.-tenth day of the disease. The number of cases observed on the first day of illness is much too small, so this has been excluded. From the figures certain tendencies may already be gathered. Above all it seems — as expected — that the number of febrile children decrease the further the disease has progressed. An indication of protracted fever can be traced with increasing age, and the figures for the three groups of only, first, and later children generally show a falling series. The result of the statistical elaboration appears from the quotients in tables I, II and III.

Table I.<sup>1</sup>

Single Children — Later Children.

Quotients:

Groups:	168.77***	35.73***	77.68***
Ages:	16.15***	3.42*	3.76***
Days:	700.22***	322.08***	162.92***

<sup>1</sup> Figures with \*\*\* represent a probability more than 999/1.000.

» » \*\* » » » » 99/100.  
» » \* » » » » 95/100.

The comparison between single children and later children in table I shows with a probability that exceeds 999/1000 that single children are more liable to get temperatures than the others. The quotients for »days» are expressive of the fact that the temperature-curve is falling during the first ten days. The fever reaction is considerably stronger with increasing age.

*Table II.*

First Children — Later Children.  
0—3 years — 12 years. Sec.-tenth day of illness.

	Quotients:		
Groups:	8.25**	2.04	6.59*
Ages:	16.08***	3.96*	3.59***
Days:	785.42***	627.74***	175.65***

On account of the more limited material within the group »first children» in the lowest age-classes the ages 0—2 and 2 years have been considered under one head in table II. The difference between the two groups is here from a statistical point of view not so certain as in table I, but there is a considerable probability (more than 99/100) that the first children show a greater disposition for fever than the later ones.

*Table III.*

Single Children — First Children.  
0—3 years — 12 years. Sec.-tenth day of illness.

	Quotients:		
Groups:	76.15***	39.20***	26.19***
Ages:	0.58	0.30	0.16
Days:	560.32***	192.71***	151.05***

In table III the influence of age does not appear as before, but the difference between the two groups of children is raised above all doubt.

The comparison between the two groups of first children divided with regard to the interval to nearest younger children can of course be undertaken only in the ages 6—12 years. There

is no reason to suspect an unequal division of age within the groups so the material has not been divided into age-groups. The computation is based on absolute figures. The children who have for a long time remained only children already in the original table seem to be more liable to become febrile than the others. This difference is statistically proved by the quotient between groups: 209.56.\*\*\*

The comparison between the two groups of later children is elaborated in the same way as regards the above-mentioned first children. The result (quotient between groups: 582.53\*\*\*) shows that the »latecomers» offer great similarities with the first-born children.

With the results hitherto given the investigation of initial temperatures in scarlatina is concluded. In the following examinations it has not proved possible to carry through the analysis regarding the five groups dealt with above. As in the case of fever reaction there seem to be similarities among single children, other first-born children, and »latecomers» it cannot be considered unjustifiable to record these under one group which to simplify matters may be described as »first-born».

In connection with the differences shown in initial fever in scarlatina an examination of the intensity of the eruption may prove of interest. On the basis of the records in the diaries the exanthema has been determined on admission to hospital and has been registered in the terms of three degrees: weak, medium and intensive. In a previous article (*Acta Pæd.* XXXI: 367) I have drawn attention to the fact that a stronger exanthema becomes more common with increasing age. This investigation gives the same result. The comparison here made between the both groups of children shows that the more intensive degrees of exanthema is more common among the first-born children. The probability, expressed in the quotient 36.71\*\*\*, exceeds 999/1000.

A question of greater practical importance than those dealt with above is whether the risks of complications in scarlet fever vary with the various groups of children. As pointed out by Dahlberg and v. Sydow (*Acta Med. Scand.* 72. 1929) it is desirable in order to avoid sources of errors in all statistics of complications

to work with risk-figures instead of the usual frequency-figures. The figures which have been statistically elaborated here therefore represent the risks of complications in percentage during the first five weeks of the disease and have been calculated in the way as appears from the abovementioned paper. As complications have been considered suppurative otitis media, lymphadenitis (though not during the first ten days), synovitis, nephritis, carditis, and infections of the upper respiratory tract.

This investigation yields with considerable probability, as shown in table IV, the result that the risk of complications decreases with age, though it is greater for the first-born children than for the those born later.

Table IV.

Risk of complications in Scarlatina.  
First-born — Later-born.

Quotient between ages . . . . .	6.98**
»            »       groups . . . . .	14.51**

Is it so that the results hitherto obtained show that first-born children present a reduced resistance to scarlet fever? As lethality in scarlatina was particularly low during the years covered by the material collected this question cannot be answered directly. It is, however, difficult to imagine that the supposed lower resistance should be reserved for only one infectious disease so the question may suitably be tested in the case of a disease with a somewhat higher lethality. With this in view the diphtheria-material at the hospital during the years 1917—1938 has been collected and elaborated.

The percentage figures for lethality are based on in all 6 246 clinical cases of diphtheria (the bacilli-carriers being excluded) 2 482 of which were first-born. In the primary table the decline in lethality with increasing age is apparent and an indication of a difference between the groups may be noticed. In some of the age-groups, at least, lethality appears to be higher among first-born children. From a statistical point of view this difference is, however, particularly uncertain why the result does not permit



any final conclusions. The quotient between ages and groups are 12.30\*\*\* resp. 4.02.

The severity of the disease can to a certain extent be deduced from the treatment of the diphtheria patients which during the said years has been adjusted according to the same principles. The greater number I. U. per ko. body-weight a patient has received the severer has the disease been considered by the physician in attendance. Statements of the patient's weight are missing in the records so the serum dosis is calculated after age and the mean-weight figures in the tables which have been drawn up by Broman, Dahlberg, and Lichtenstein. The result shows with a statistically satisfactory security that the first-born children have received more serum than the others. The quotient between groups is 90.29.\*\*

The serum dosage cannot, however, be said to offer any proof that the first-born children have been more seriously ill than the others. The reaction of single children — and their parents — may in the first line have induced the physician to consider the situation as more serious than necessary. The result obtained is, however, of importance for the answering of the next question.

The scarlatina material examined showed that the first-born children reacted more strongly, as far as regards temperatures, and also by way of stronger eruptions. In these circumstances it lies near to examine whether this disposition for reaction also applies to the serum disease. To judge by existing literature the magnitude of the dosis certainly influences the frequency of the serum reaction, on the other hand the influence of age seems more doubtful. In judging these two factors frequency-figures have hitherto exclusively been applied which for various reasons may be misleading as they to a great extent must depend on the length of the observation-period. It is also in this case necessary to work with risks.

The calculation is based on figures representing the risk in percentage during the first 24 days after the first serum injection. The total number of cases is 7 864. The result shows that the risk of serum disease increases with age as well as with increased dosis which is statistically secured by the quotients between ages

and doses 28.54\*\*\* resp. 85.00.\*\*\* As it has already been shown that the first-born children received larger amounts of serum than the others it is necessary to consider the age as well as the serum dosis by testing any possible difference of risk for the two groups of children.

*Table V.*

Serum Disease.  
First-born — Later-born.

Quotients:			
Groups:	33.48**	6.82	13.42
Ages:	0.27	0.06	0.64
Doses:	19.39**	7.79	45.44**

The investigation resulting in table V cannot prove any difference between the age-groups, which probably is due to the fact that the increased disposition for serum disease only appears at higher ages than those included in this examination. The difference between the groups which shows a tendency for the first-born children to get serum disease more often than the others cannot be said to be fully statistically proved but remains probable.

We have thus with a reasonable degree of probability been able to show that the first-born children more often react with fever and with stronger eruptions in the case of scarlet fever. The risk of complications in this disease is greater for first-born than for later-born children. In cases of diphtheria the first-born children have received larger doses of serum but they have not with certainty been proved to show a higher lethality than the later children. On the other hand they possibly represent an increased disposition for serum disease.

In a discussion concerning the reasons of these particular characteristics in first-born children it is only the special question of the initial fever in scarlatina that permits a more thorough analysis. Nevertheless it appears probable to me that all the qualities found must be traced back to a common reason. If this supposition is correct the arguments advanced concerning the

fever reaction might be applied also to the other qualities even though the material has not in all cases made it possible to carry group-division of the children equally far.

Hereditary factors might be supposed to prevail in the case of single children. Parents with only one child may possibly differ constitutionally from others. This cannot, however, be the cause of the phenomena found, for first-born children with younger sisters and brothers indeed offer the same — though less marked — qualities in their fever-reaction as single children. On account of the difference shown between first children who are considerably older than their nearest following sisters and brothers, and the first-born with slight intervals in age, the question may be raised that it is only a case of a difference in degree between families with one child and such families in which the children are born with long intervals. But why is it in that case that the first-born children who already after some years are followed by younger children differ from the later-born children?

The first-born are to a greater extent than other children underweighty at birth and certainly also more exposed to obstetrical injuries than other children. This reason, however, leaves the »latecomers'» conduct unexplained, nor does it conform with the abovementioned difference between the two groups of first children.

All kinds of infections which no doubt are more common among children that belong to a greater ring of sisters and brothers and therefore probably more often descend on the later children might be supposed to create an unspecific immunity. In this way their reaction, also in the case of specific infections, as for instance scarlet fever might be influenced. Single children and first-born children with long intervals to nearest following sisters and brothers have grown up in environments that to a smaller degree have exposed them to infections from outside sources. Even on this hypothesis it nevertheless remains inexplicable why »latecomers» behave like first-born children. The children whose nearest elder sisters and brothers are more than seven years older than them are nevertheless from their earliest infancy liable to catch infections carried into their homes. This presumed immunity

ought accordingly to apply to these youngest children to the same extent as to the other later-born children.

In whatever way the problem is considered the most probable reason is in my opinion the particular environment of the first-born child. The thorough change in the way of life and outlook of the young family, which the arrival of the first child involves, the parents' and above all the mother's uncertainty in face of the new problem, the often failing psychical balance in the woman bearing her first child, all these factors co-operate to form a special atmosphere round the new-born child. The ancient principle of primogeniture is not a conventional idea either. For most parents the first child will as a rule occupy a particular position which becomes more marked the longer the time that passes before the interest is divided on the following children. If the child remains the only one these conditions become still more marked. The »latecomer» grows up surrounded by grown ups and young people and is encompassed with an anxiety and a care on the part of the parents that is somewhat similar to their attitude towards their grandchildren.

It is well-known to every pediatrician that children that have grown up under conditions as those sketched here to a greater extent than others offer neurolabile characteristics. Wallgren has in his article that is so rich in observations on neurolability in children (Sv. Läkartidningen 38: 765) indicated that the neurolabile peculiarities are often found in first-born children. In the same article he mentions a biological inferiority in the neurolabile child. Possibly the phenomena dealt with in this paper are dependent on the varying frequency of neurolabile children within the various groups. The examination has not, however, yielded a definite answer to the question whether the qualities found simply express a larger reaction-amplitude in the first-born children or whether the latter show a reduced resistance to infection. The larger doses of serum make us suspect that the first-born children really have been more ill of diphtheria than the others, but it is also possible that they through their general appearance have given the doctor the impression of a severer attack of the disease than was actually the case. The increased

risk of complications in case of scarlet fever ascertained, however, appears to me to be in favour of the opinion that reduced resistance is the cause of the phenomena found.

At any rate the result of the investigation presented here seems to me from a practical standpoint to elucidate an important quality in first-born children. Possibly the result may further be used in support of the view that environment may give rise not only to psychical, but also to somatic peculiarities in children.

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FROM THE PEDIATRIC CLINIC OF KAROLINSKA INSTITUTET AT KRON-  
PRINSESSAN LOVISA'S CHILDREN'S HOSPITAL, STOCKHOLM.  
HEAD: PROFESSOR A. LICHTENSTEIN.

## **Acute Rheumatic Infection in Children.**

### **Clinical Studies with Special Reference to the Initial Phase and the Valuation of the Cardiologic and Hematologic Signs.**

By

**AXEL FRIEDLÆNDER.**

It is generally known that the rheumatic symptom complex in childhood progresses different to adults, especially in the initial stage. Joint findings are often slightly pronounced, local changes in joint structure negligible and monarticular appearance not uncommon. Heart complications can develop unobtrusively without simultaneous or previous swelling of the joints and without attention being drawn to the heart. The rheumatic carditis belongs to the more dramatic and tragic accidents particularly because it is so often neglected in the beginning. HOLT and McINTOSH (9) have appropriately expressed their view of the rheumatic infection in children, when they say: »In order to recognize it one must free one's mind from the picture of the disease as it exists in adults.»

The last years' systematic electro- and phonocardiographic investigations have expanded our experience with regard to the progress, frequency and localisation of the rheumatic carditis. By phonocardiography a more exact and objective valuation of the stethoscopic findings has been possible and especially in the study of gallop rhythm the method of phonocardiography has been of considerable value. In the following I will discuss certain characteristics of acute rheumatic infection with special regard to the initial stage.

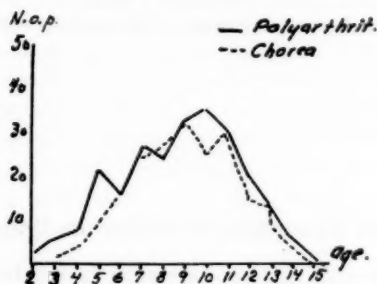


Diagram 1.

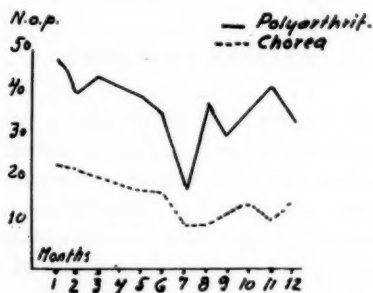


Diagram 2.

The material dealt with comprises altogether 446 children from 3—15 years of age, who during the period 1914—43 have been treated at K. L. children's hospital for acute rheumatic infection. The polyarthrit. group consists of 248 (132 boys, 116 girls), the chorea group of 198 (132 girls, 66 boys). In a smaller group of patients (83) from the period 1933—43 more details regarding cardiac involvement are at hand, as in these cases combined electro- and phonocardiography have been performed.

*The age division* (Diagr. 1) is on the whole in accordance with KARLSTRÖM's (12) material from Stockholm comprising 924 children. The frequency of polyarthrit. is greatest between the ages of 7 and 11, of Chorea between 8 and 11 years. *The year division* (Diagr. 2). Chorea shows a greater increase at the be-

ginning of the year, whereas polyarthritis has two maxima: spring and autumn. *Family disposition.* Recent research has stressed the importance of heredity. T. KEMP (14) (1943) alleges that in about one third a rheumatic infection is shown in other members of the family, even if no common infection or other uniform outside influences seem to exist.

In this material the figures of family disposition are divided as follows:

Table I.

	Total number of cases	Previous rheum. inf. in the family	
		Number of cases	Percentage
Polyarthritis . . .	248	70	25
Chorea . . . . .	108	14	7

A *nervous disposition* (mental disease, depression, neurasthenia) in the family of choreic patients is not uncommon. In 26 cases a nervous state is proved among the parents (14 %). 15 of the choreic children were psychic debile. In addition, 4 suffered from Enuresis, 2 from Migraine, 3 had Pavor nocturnus and 2 Recurring acidotic vomiting.

*Mortality.* 20 children (4.5 %) died in hospital of rheumatic infection. The cause of death was in the majority of cases a progressive malignant endo-myo-pericarditis. *Recurrence* occurred in polyarthritis is 23 %, in Chorea in 42 % (Chorea recurred in 46 cases as Chorea, in 37 with joint symptoms). The recurring percentage for the whole material is 31, i.e. hardly one third has had any form of recurrence.

*The initial phase.* Especially American authors (COBURN (1—2) a. o.) have described the phases of the rheumatic complex. The first phase is one of acute tonsillitis. The second is characterised by almost complete absence of clinical symptoms. (»The free interval.«) The third phase is the period of the actual rheumatic manifestations.

The importance of the *tonsils* for the rheumatic infection has



always been the subject of discussion and the question of tonsillectomy has been argued for and against. It may therefore be of interest to examine 1) how often evidence is found of initial tonsillitis and 2) how frequently the tonsils are the seat of definite chronic inflammatory changes.

Referring to 1). In 260 cases of acute polyarthritis definite anamnestic information is found. In 96 (46 %) an acute tonsillitis was present in the initial stage. As to the remaining 164 it is explicitly mentioned that the initial tonsillitis is lacking. In 62 (of 96), furthermore, a distinct »free interval» is present between the tonsillitis and the rheumatic manifestations, as a rule a period of 8—14 days, during which the child is in apparent good health. When admitted to hospital, the tonsillitis has frequently vanished and only little — if any — signs of inflammation is to be seen. The »free interval» is so often and unanimously described in the case reports that it should be regarded as characteristic.

The question of the tonsils is more difficult to make clear in chorea because the symptoms here are developing in a more insidious manner. As the choreic patient is often admitted to hospital later in the course, the anamnestic informations regarding tonsillitis are not seldom unsatisfactory. In 46 choreic cases 24 (about 50 %) had an initial tonsillitis. As 10 were complicated with polyarthritis, there only remain 14 cases of chorea in which a definite tonsillitis in the initial phase was present.

*Chronic tonsillitis.* When seeking information on this subject one is inevitably confronted with the difficulty of finding an exact definition. A simple hyperplasia does not, of course, express whether a chronic inflammation is present. KAISER (10—11) defines tonsil hyperplasia in the following manner: »A truly hypertrophied tonsil is one, in which there is a marked increase in size due to rapid and abnormous growth of tissue.» Tonsil hyperplasia is often a result of infection, but a hyperplasia is in numerous cases found without any infection at all. Terms as »enlarged» are of course not at all explicit. I have therefore classified tonsil hyperplasia in a group of its own and limited the term chronic tonsillitis to those cases in which an enlargement and cleavage

of the tonsils with »pus spots» in the crypts — also when no signs of acute exacerbation are found. (In addition further evidence is found in frequently recurring acute tonsillitis and — eventually — inflammation of the cervical glands.)

The result of the statement is as follows: Among 318 patients (polyarthrititis 162, chorea 156) a chronic tonsillitis was present in 33 (about 10 %) (Table II).

*Table II.*

The frequency of Tonsillitis chron. in Polyarthrititis ac. and Chorea.

	Cases	Normal	Hyperplasia tonsill.	Tonsillitis chron.
Polyarthrititis acuta . .	162	90	54	18 (11 %)
Chorea . . . . .	156	114	27	15 (10 %)

If the frequency of tonsillitis chron. in the cases where the rheumatic infection has started as an acute tonsillitis is compared with those, in which the initial tonsillitis is lacking, the figures divides in the following way:

*Table III.*

	Cases	Normal	Hyperplasia tonsill.	Tonsillitis chron.
<i>Polyarthrititis ac.</i>				
+ initial tonsillitis . .	66	25	27	14 (21 %)
÷ initial tonsillitis . .	87	64	23	0
Initial tonsill. not mentioned . . . . .	9	1	4	4
<i>Chorea.</i>				
+ initial tonsillitis . .	26	12	4	10 (38 %)
÷ initial tonsillitis . .	121	98	23	0
Initial tonsill. not mentioned . . . . .	9	4		5

It is worth noticing that *all the cases of chronic tonsillitis are found in the group, in which an acute tonsillitis preceded the rheumatic manifestations.* Accordingly it must be allowed to assume a connection between the presence of chronic tonsillitis and initial angina.

*Tonsillectomy* has been performed on 46 patients. In no case the operation was able to prevent rheumatic attacks in the following years. (Table IV.)

Table IV.

Acute rheumatic infection after tonsillectomy (46 cases) of 46 tonsillectomised children.

	Years after operation			
	1	2	2—5	> 5
26 were attacked by polyarthritis . . .	9	3	9	5
20 were attacked by chorea . . . . .	11	2	4	3
Total	20	5	13	8

It should further be emphasized that 10 children contracted polyarthritis, carditis or recurring chorea in direct connection with the tonsillectomy. The case reports urge the greatest caution and warn against operating rheumatic children without due consideration, especially if late clinical examinations show even the slightest sign of rheumatic activity. The discouraging results are in accordance with American examinations on a larger scale.

WILSON, LINGG and CROXFORD (30) thus examined the results of tonsillectomy in 413 children, who had suffered from one rheumatic attack. It was shown, that children under 9 years of age were just as frequently attacked by a recurrence whether or not they had been tonsillectomized. After 10 years observation recurrence was less frequent in both groups. KAISER (10) comes to more or less the same result. The indications for tonsillectomy should be limited to cases where a definite tendency to recurrent angina is present. The fact, that a chronic tonsillitis is only pointed out in cases, where the rheumatic disease is preceded by

acute tonsillitis, and the evidence of an initial angina in about half of the material presented here, confirms this opinion.

*Abdominal pain* is a prevalent symptom in the initial phase. The attacks can be so severe that they may result in erroneous diagnosis. No less than 23 children (9.4 %) presented this symptom, 8 were admitted for acute appendicitis, in 3 laparotomy (with normal appendix) was performed. The cause has not yet been revealed. In some cases peritoneal reaction is found, in other small hemorrhages in the mesentery glands. It must however be emphasized that the signs often are negative (TAUSSIG (24)).

*There is reason to stress the possibility of a rheumatic infection in every case of abdominal pain in children.* When the symptom is present in nearly 10 %, it is surprising that some text-books and monographies do not sufficiently emphasize the fact.

*Monarticular arthritis* (by which is understood not only that the rheumatic disease begins in a single joint, but also its remaining monarticular for some time) has been observed in 17 cases (about 17 %). It is mostly the hip joint that is affected (10 out of 17 cases). The knee joint was affected in 4, the ankle twice and the elbow once. In 7 cases a monarticular right-sided rheumatic coxitis was mistaken for an appendicitis.

*Meningeal and cerebral complications* are, with the exception of chorea, rare. In one case the localization of the rheumatic process to the cervical spine led to the false diagnosis of an meningeal affection.

#### *The Cutane (and Subcutane) Manifestations and their Diagnostic and Prognostic Value.*

Four varieties are included: Erythema annulare (E. a.), Erythema exudativum multiforme, Erythema nodosum and Noduli rheumatici. Of these, according to WALLGREN (27), erythema annulare and nod. rheum. are pathognomonic. Of special interest is his statement of erythema annulare as the first symptom and that the presence of the affection can prove the diagnosis so early, that the blood sedimentation rate is not yet raised. It must

therefore be regarded as a professional mistake not to examine every patient suspected of rheumatic inf., with reference to E. a. This is especially applicable when no changes in the heart can be revealed. WALLGREN finds, however, E. a. only in 12 % in the period 1931—34. The diagnostic value of the symptom is thus reduced by its comparative rarity, especially in Scandinavia. I have only been able to find 9 convincing cases of E. a. (3.6 %). (In comparison it may be added that LEICHTENTRITT in a material from the Breslau clinic has noticed E. a. in no less than 62.5 %.) That the symptom nevertheless can be of the greatest importance for the diagnosis is evident. One of the patients with E. a. was on account of severe abdominal pain suspected of acute appendicitis. On the day after admission, however, a typical E. a. was observed. This, in connection with the remarkable high sedimentation rate, made a rheum. inf. highly probable, although joint involvement were only slight. My cases (Table V) confirm the opinion held in particular by German clinicians: *E. a. suggests an imminent carditis* (LEINER, LEHN-DORFF (15), LEICHTENTRITT (16—17)).

Table V.

Erythema annulare (9 cases).

Cases	Diagnosis	Heart involvement	Appearance of erythema
1	Polyarthritits	Endocarditis mitral. a. aort.	8 days after polyarthritits
2	"	Endocarditis	14 " " "
3	"	Endo-myocarditis	10 " " "
4	"	Endocarditis	4 " before "
5	Pancarditis	Pancarditis	3 weeks after carditis
6	Polyarthritits	Endocarditis; 6 months later severe endo-my-pericarditis	6 " " "
7	"	Endo-myocarditis	12 days after "
8	"	Myocarditis	7 " before "
9	Pancarditis	Endocarditis (gallop rhythm)	4 weeks after "

*E. a.* has only twice appeared so early that the erythema has been of value as »an early symptom». The case histories all indicate the importance of *E. a.* as far as the prognosis is concerned.

*Rheumatic nodules* have only been observed in 6 cases (1.3 %) all suffering from serious rheum. infections.

Table VI.

Rheumatic nodules (6 cases).

Cases	Diagnosis	Heart involvement	
1	Polyarthrit. Chorea	Endo-myocarditis. Gallop rhythm	
2	Polyarthrit. Chorea	Endocarditis mitral. a. aortae Pericarditis	Dead
3	Polyarthrit.	Endocarditis mitral. a. aortae	Multiform erythema. Dead
4	"	Endocarditis mitral.	Multiform erythema.
5	"	Endo-myocarditis	
6	"	Myocarditis	

*Erythema exudativum mult.* is also represented by 6 cases — two in addition having rheum. nodules; these and the remaining 4 were all suffering from severe pancarditis. The erythema exud. mult. (as well as the rheum. nodules) made their appearance late in the course of the disease and took — in contrast to *E. a.* — a long time to disappear. One can therefore suppose that the *multiform erythema* — like *E. a.* — in some way is connected with the rheumatic infection and suggests a serious prognosis. (*E. a.* and *Erythema multiforme* have not been simultaneously observed.)

Table VII indicates that *E. a.*, *E. exud. mult.* and rheum. nodules during the period 1914—43 have been stated in 21 cases (thereof 15 between 1914—35). After 1935 *E. a.* has only been observed 4 times, mult. erythema and rheumatic nodules each once. *Rheumatic nodules* have not been noticed since 1940. These figures are strikingly low considering partly, that all

Table VII.

Frequency of Erythema annulare, Erythema exud. multiforme and rheum. nodules in the period of 1914—43.

Period	Erythema annulare	Multiform Erythema	Rheum. nodules	Total	Dead
1914—24	2	2	4	8	2
1925—35	3	3	1	7	3
1936—43	4	1	1	6	0
	9	6	6	21	5

rheumatic patients — espec. during the last ten years — have been systematically examined with special regard to the above, partly because the number of rheumatic patients has increased of late. The figures are of course too low to decide whether the cause may be explained by the possibility that the rheum. polyarthritis has become more benign; nevertheless it is remarkable that among 20 children who died in the clinic, not less than 16 belong to the period of 1914—35 (thereof 13 between 1914 and 1928). Since 1934 only 4 children died of rheumatic disease. It is my opinion that polyarthritis in children have become milder and of a shorter duration.

*Erythema nodosum rheum.* has only been observed twice (0.4 %). The two cases both were tuberculin-negative and had a definite and typical rheumatic pancarditis. No other cause of the affection could be stated (WALLGREN (25) (1938) only relates one case among 800 (0.1 %)).

#### The Heart.

*Rheumatic carditis* has earlier been regarded as a complication — a secondary manifestation. The fact is however that the carditis often especially in children is the first rheumatic manifestation. As LEWIS (19) puts it: »To regard the joints as the primar or central point of the disease is to go beyond the facts.» The primary rheum. carditis is nearly always a serious illness with a doubtful

prognosis. It often begins in an insidious manner and may be difficult to recognize. Owing to the characteristic pale appearance, the diagnosis may be mistaken and the child thought to have anaemia, dyspepsia or simply to be in a general poor condition. Pain in the precordial region or epigastrium, loss of weight, fatigue are current symptoms. After thorough inquiry however the doctor will frequently be informed about inconstant pain in the joints and perhaps *slight choreatic disturbances* which are easily disregarded or diagnosed as »tic» but in some of my cases have been an *important indication of the true nature of the disease*. In one case a typical erythema annulare was observed immediately previous to the clinical examination revealing an endo-myocarditis with gallop rhythm.

Altogether 20 cases of primary carditis were observed (4.5 %). 4 died.

The clinicians have formerly attached great importance to auscultation and considered a systolic murmur a decisive indication of the acute rheumatic endocarditis. WARBURG (28) warns however against diagnosing the isolated mitral insufficiency merely on auscultation. In several cases the systolic murmur — in the course of a rheumatic infection — must be considered as an »intonation sound», not as a sound of insufficiency. By means of Phonocardiography MAC KEE (13), E. MANNHEIMER (20, 21, 22) a. o. have stated that *a systolic murmur is present in the great majority of normal cases*. The diagnosis rheumatic carditis, therefore, must be confirmed by other clinical methods particularly combined electro- and phonocardiography.

In recent investigations FRIEDLÄNDER and MANNHEIMER (5) compare the frequency and amplitude of the systolic murmur in acute rheumatic fever partly with normal cases and partly with children suffering from congenital heart disease. It is hereby shown that the systolic murmur in ac. rheum. inf. often has the same amplitude as in the normal heart, whereas the amplitude in congenital vitum is always greater. In about half of the rheumatic cases the frequency lies at the same level as normal. That is to say: It is often difficult to recognize acute rheum. carditis only by auscultation and phonocardiography, because the frequency of



the rheumatic systolic murmurs often are localized within the normal zone (50—250 vibrations per sec.), as in 25 of 32 phonocardiographically examined cases. The matter is on the other hand quite different as to the diastolic murmur. A diastolic murmur does not appear under normal conditions and seldom together with a congenital vitium. A diastolic murmur therefore ensures the endocarditis diagnosis (LICHTENSTEIN, MANNHEIMER a. o.).

The phonocardiographic registration of the gallop rhythms, finally, renders valuable assistance in the early diagnosis of the rheumatic endocarditis. Three kinds of gallop rhythm (MANNHEIMER (20)) are generally recognized:

1) Third sound gallop occurs when the rate and amplitude of the third heart tone are enlarged: It is formed by the inrush of blood against the ventricular wall at the beginning of diastole («The Phase of rapid filling»). It is, as a rule, connected with myocardial involvement and acute dilatation of the ventricle and is of benign nature.

2) Auricular sound gallop (atric tone gallop) is due to a dilatation of the atrium. It most frequently occurs at the initial stage of endocarditis mitralis together with dilatation and hypertrophy of the left atrium. It is an unfavourable sign from a prognostic point of view.

In 3) Summation gallop there is a summation of 1) and 2) by shortening of the diastole (in tachycardia or prolonged p—q interval). The prognosis is here also doubtful.

Combined electro- and phonocardiographic examinations were performed on 83 patients. The results can be summarized as follows: In 22 cases both systolic and diastolic murmurs were registered. In 9 of these cases the diastolic murmur was affirmed by the phonocardiographical examination alone. Gallop rhythms were revealed in 19 cases (in 7 as third-tone gallop, 5 as auricular tone gallop and in 7 as summation gallop). *Only in 7 cases of 19 the gallop rhythm was recognized by means of auscultation.* In 9 cases of auricular sound gallop and summation gallop dilatation of the atrium was verified by roentgen examination.

There can accordingly be no doubt that the phonocardiographic examination is of great importance in the diagnosis of the rheu-

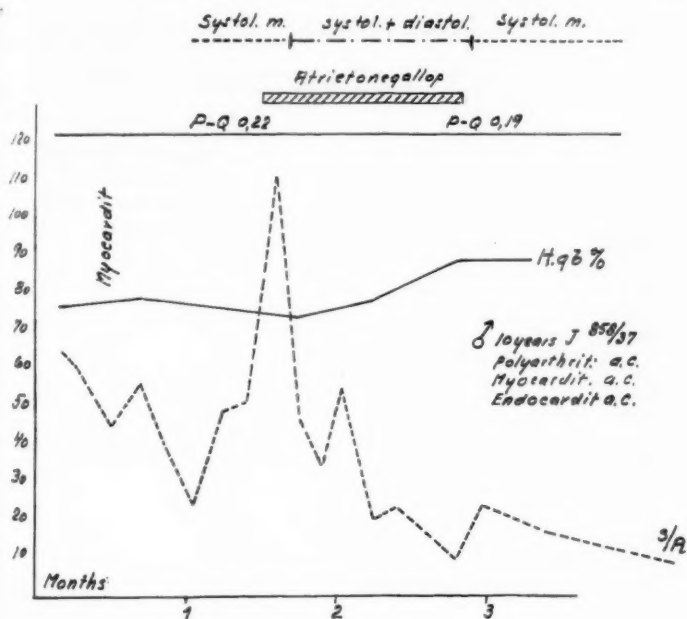


Diagram 3.

matic endocarditis particularly in the early stadium of the disease: Definite changes in the electrocardiogram were stated in 72 of 83 patients. In all 76 (of 83) showed clear signs of rheumatic carditis.

In order to stress the importance of phonocardiography in valuation of the heart involvement, a few typical case reports may be quoted.

Boy, 10 years of age. J. 858/37 (diagram 3). Clinical diagnosis: polyarthrit. ac. rheum. endo-myocarditis ac. (gallop rhythm).

During the course of an acute polyarthrit. a myocarditis develops. The p-q interval is prolonged and the sedimentation rate considerably increased. The condition gradually improved and the sedimentation rate returned to normal. A systolic murmur was registered within the normal frequency zone. After a fortnight the Fkg showed a pronounced gallop rhythm (auricular sound gallop), but no diastolic murmur. After

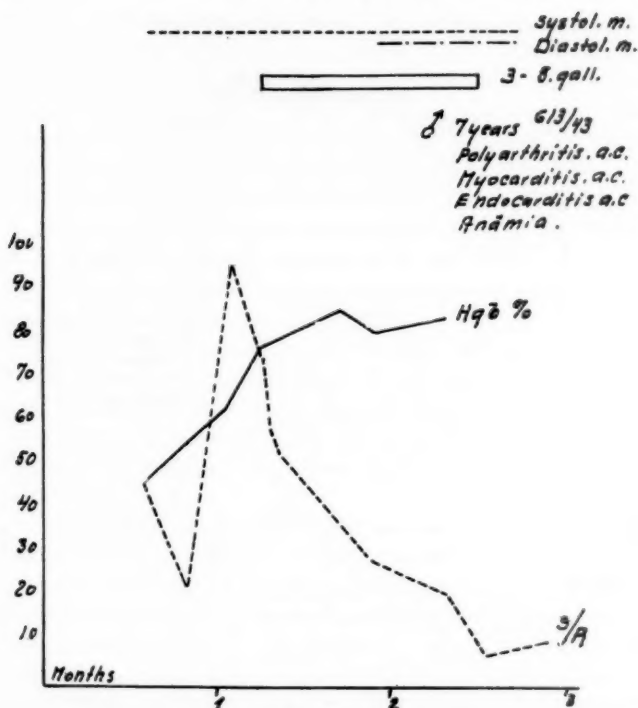


Diagram 4.

another 10—12 days the diagnosis endocarditis mitral. was confirmed in the Fkg by a clear pre-systolic and protodiastolic murmur. The sedimentation rate gradually decreased and both the gallop rhythm and the diastolic murmurs disappeared. During reconvalescence only a systolic murmur was registered. The hemoglobine value remains between 70 and 80 with some tendency to rise before the regression of the endocarditic process. Roentgen examination gradually showed dilatation of the left atrium, which was later reduced.

Boy. 7 years of age. J. 613/43 (diagram 4). Clinical diagnosis: polyarthritis ac. rheum. myocarditis. Anaemia (gallop rhythm).

On admittance the Ekg shows evident signs of myocarditis and the Fkg a systolic murmur in the frequency zone of 50—300. The sedimentation rate is high. Gallop rhythm appears (third tone gallop). No

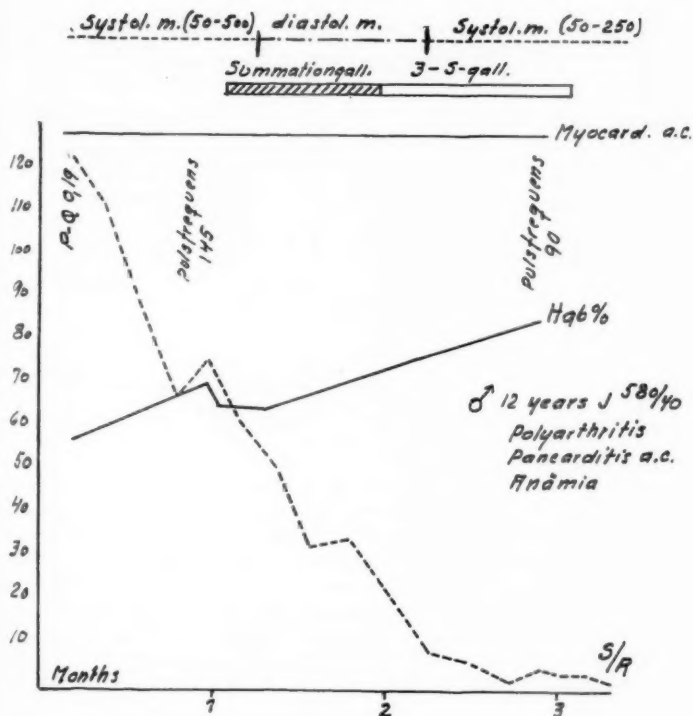


Diagram 5.

diastolic murmur either in the Fkg or by auscultation. After about 6 weeks the Fkg showed a diastolic murmur, which was proved later by auscultation; roentgenologically a dilatation of the atrium was stated. The case illustrates the value of the gallop rhythm appearing before the diastolic murmur giving warning of the imminent endocarditis. The anaemia disappears and it is worth noticing that the increase in hemoglobine value continues during the period of endocarditis.

Boy, 12 years of age. J. 580/40 (diagram 5). Clinical diagnosis: polyarthritis ac. Pancarditis ac. (gallop rhythm).

An acute polyarthritis is followed by a myocarditis (p—q interval slightly prolonged). The Ekg shows improvement and the sedimentation rate decreases. About 2 weeks later tachycardia and gallop rhythm (sum-

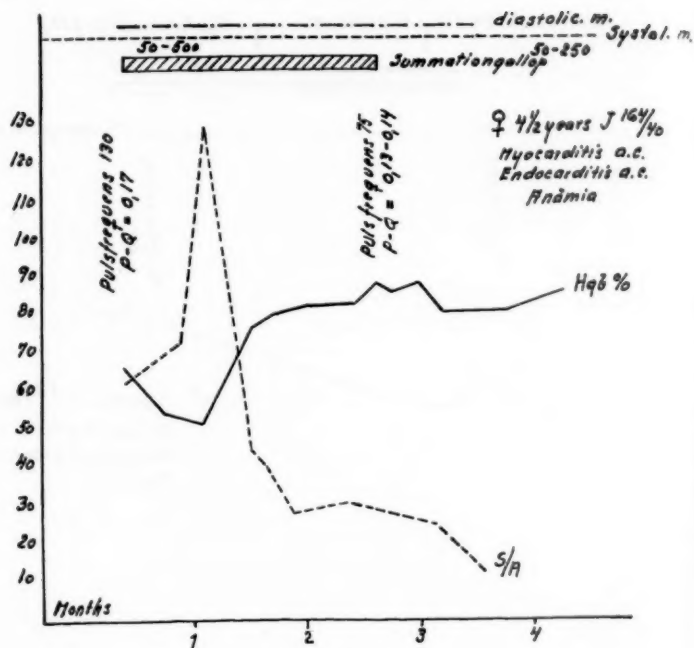


Diagram 6.

mation gallop). After 6 days protodiastolic murmur. After another 4 weeks the gallop rhythm changes and is now registered in the Fkg as a third tone gallop. Simultaneously the protodiastolic murmur disappears while the systolic murmur remains unchanged in the frequency zone of 50—250. After another 3 weeks the third tone gallop disappears. Only a faint systolic murmur remains.

The gallop rhythm is here on account of the increased pulse rate and the prolonged p—q interval registered in the Fkg as a summation gallop. Gradually as the condition improves the summation gallop gives way to the more benign third tone gallop. The disappearance of the diastolic murmur is a further evidence of the receding endocarditis. The hemoglobine value decreases when the gallop rhythm aggravates the condition, but is later increasing, although the gallop rhythm has not yet disappeared.

Girl. 4 years of age. J. 164/40 (diagram 6). Clinical diagnosis: Endomyocarditis ac. rheum. Anaemia (gallop rhythm).

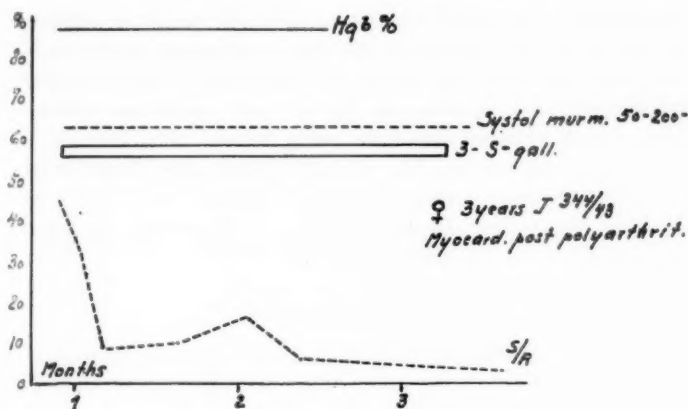


Diagram 7.

A sudden aggravation occurs in the course of an acute rheum. myocarditis with moderate Ekg changes (tachycardia and prolonged p—q interval). At the same time a gallop rhythm (summation gallop) and a diastolic murmur is registered in the Fkg. Further a systolic murmur is present in the frequency zone 50—500. After about 3 weeks both the systolic and diastolic murmurs are less pronounced. The sedimentation rate is decreasing. The gallop rhythm remains unchanged. One month later the gallop rhythm vanishes. After another 3 weeks the diastolic murmur disappears as well. On dismissal only a faint systolic murmur of low frequency is demonstrable.

The gallop rhythm and the diastolic murmur in this case appear simultaneously together with the development of a considerable anaemia. It is of further interest that the anaemia disappears already at a time, when the Fkg signs are still well pronounced.

At last a brief case report (diagram 7) illustrating the mild character of the third tone gallop. The gallop rhythm remains unchanged during the whole time of observation. No diastolic murmur is registered and the sedimentation rate is steady and low. The normal hemoglobine value is a further proof of the benign nature of the heart involvement.

These typical cases affirm that phonocardiography, besides revealing a gallop rhythm at a time when nothing can be heard by auscultation, also is able to determine the type of gallop rhythm dealt with. It is known that it is not possible to distinguish the third tone gallop from the auricular tone gallop by means of

auscultation. As the auricular tone gallop is a result of dilatation of the atrium it is clear that the phonocardiogram is able to give important diagnostic and prognostic information. Repeated phonocardiologic examinations can further give important details in verifying the endocarditis in an early stage.

Concluding I should like to state: In the early demonstration of the acute endocarditis phonocardiography yields more than electrocardiography. In the diagnosis of myocarditis the electrocardiogram gives the best information.

*Table VIII.*

Frequency of Heart Complications (in the total Material).

	Number of Cases	Heart Com- plications	Percentage
Polyarthrit. ac. . .	248	181	73
Polyarthrit. + chorea	55	41	74
Chorea . . . . .	143	38	26
Total	446	260	58

The reason for the low carditis percentage in the total material is partly because EKG and FKG in earlier days were not performed in a number of cases, partly because the examinations were not made daily, and finally because chorea is in a more favourable position as far as heart complications are concerned. If chorea however is complicated with polyarthrit. the number of heart complications rises so suddenly that the percentage is equal to the polyarthrit. *It therefore seems to be the joint affection which plays the most important part in the frequency in which the heart is involved:*

The accounts of the frequency of the appearance of heart complications vary considerably: IBRAHIM 60—80 %, FEER 80—90 %, the Vienna clinic about 45 %, Breslau clinic 65 % (16), American statistics 95 % (COHN and SWIFT (3)). SCHERF and BOYD (23) (1943) write: »In cases of rheumatic fever, electro-cardiographic examinations, when repeated daily for a period, have shown that the myocardium is affected, at least temporarily, in the course of every rheumatic disease.»

With regard to *Chorea* it is usually stated that cardiac complications are found in about 50 %, though often only by recurrence (LICHTENSTEIN (18)).

Examination concerning the frequency of *Carditis* in resp. *Polyarthritis* and *Chorea* after the first rheumatic attack gives the following division of figures:

Table IX.

	Number of cases	Carditis after first attack	Percentage	Percentage of carditis in whole material
Polyarthritis acuta .	181	131	72	73
Chorea . . . . .	96	20	20	26

I. e. 72 % of the polyarthritis-cases contract carditis during the first attack, while the corresponding figures for chorea are only 20 %. The low percentage in chorea could possibly be due to the fact that choreic carditis appears later in the course — eventually during the relapses. Numerical investigations, however, as to the frequency of carditis in resp. first, second, third etc. choreic recurrence, give no reliable results, because it is impossible to ascertain when the carditis has made its first appearance. Among the children are several who have sustained until 4 choreic attacks without any demonstrable involvement of the heart. If, on the other hand, the above mentioned figures are compared with the carditis percentage in the total material (both of polyarthritis and chorea) a remarkable similarity is found. It therefore seems probable that the low figures found in chorea must be due to the lesser frequency of choreic carditis.

On the whole the choreic carditis is described as much more benign. The electrocardiographical examination often reveals slight but undoubted changes, when, with the use of roentgen, auscultation etc., no abnormality of the heart can be found (HEFFER (8) a. o.).

Finally therefore I have connected 25 cases of uncomplicated chorea with 8 of chorea + polyarthritis as to obtain an idea of



the frequency and nature of the heart changes in the two groups concerned (Table X). EKG is performed in all 33 cases, FKG in 17. All cases are roentgen-examined.

Table X.

Heart changes in Chorea + polyarthrititis and uncomplicated Chorea.

	Normal	Endo- myocarditis	Myocarditis
1) Uncomplicated Chorea (25 cases)	15	2	8
2) Chorea + polyarthrititis (8 cases)	0	6	2

The figures (in 1.) show no signs of heart involvement in more than one half of the cases. The 8 cases of myocarditis were all slight. (In 2 cases the process was found to be healed on re-examination two years later. In 4 the changes in EKG already disappeared before dismissal from hospital. Only two contracted a chronic vitium cordis.) *Gallop rhythm was not stated at all* and the systolic murmurs were all registered within a zone of frequency not regarded as pathological.) In the other group (2) *definite signs of carditis were shown in all 8 cases. In 3, further, gallop rhythm was revealed.* Although the figures are small, there seems to be no doubt that *heart changes in uncomplicated chorea are less frequent and more benign.*

*Acute pericarditis* is represented by 32 cases (7 %). The complication was observed exclusively in children with very severe cardiac disorders — in several cases together with a (left-side) pleural exudate. 9 died. The division is as follows:

Table XI.

	Number of cases	Pericarditis	Dead
Polyarthrititis .	248	23	7
Chorea . . . .	198	9	2

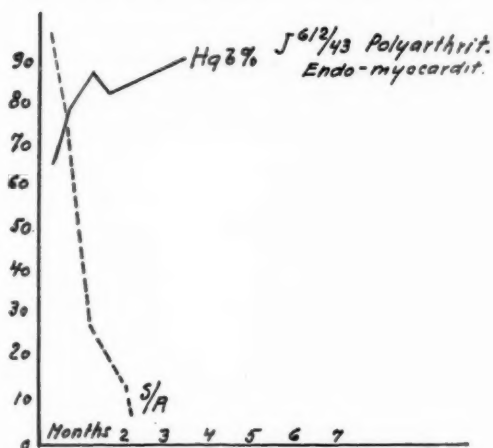


Diagram 8.

The rare combination of polyarthrititis and chorea appearing simultaneously has only twice been observed.

#### *The rheumatic anaemia.*

*Polyarthrititis acuta.* During the period of 1933—43 a hemoglobine value less than 70 % was stated in 31 cases (of 101, i. e. about 30 %). That is a comparatively low figure considering the frequency of heart involvement. GEZELIUS (7) found 70 % by weekly examination. As the hemoglobine tests on my patients are carried out with a greater interval (2—3 weeks), the results are not directly comparable. As a whole GEZELIUS' cases seem to be of a more serious nature than the material presented here (27 of 31 had definite clinical signs of heart involvement). The majority of the slight often temporary myocarditis usually shows a hemoglobine percentage within the normal. If an anaemia is present, the hemoglobine value — provided that the disease is progressing favourably — as a rule quickly increases. In some cases the rise in hemoglobine is so rapid, that the sedimentation rate has not yet become normal, i. e. anaemia often vanishes already in the active phase (diagram 8).

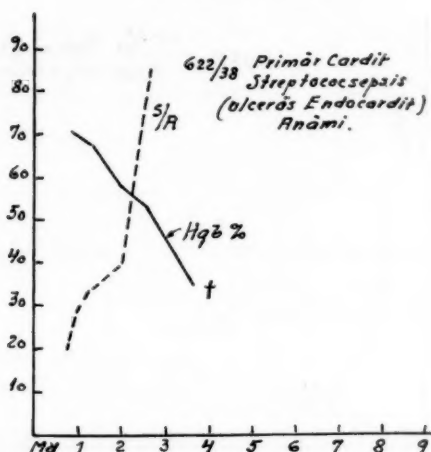


Diagram 9.

If an endocarditic process progresses fatally, the curves run in a characteristic »opposite» course. The disastrous fall in hemoglobine, together with the increase in sedimentation rate in an instructive manner illustrates the serious nature of the disease (diagram 9). If phonocardiography has revealed gallop rhythm the hemoglobine values present an interesting conformity with what was mentioned above on the prognosis. In 19 cases of gallop rhythm 10 had normal hemoglobine values. A hemoglobine value below 70 % was found in 7 (out of 12) patients with auricular sound gallop. Of 7 with three tone gallop only 2 were anaemic. Although the cases from this clinic to a certain degree confirm the opinion of WALLGREN (26) and GEZELIUS (7) regarding the importance of endocarditis as an anaemic factor, the progressive and protracted anaemia is here almost exclusively observed together with severe cardiac involvement.

**Chorea.** Among 35 choreic patients only 4 were found to be anaemic (11 %). In these (4) cases the chorea appeared secondarily during the course of a severe polyarthrititis. 3 further showed definite signs of heart involvement. Chorea has thus shown little — if any — decrease in hemoglobine value, and in

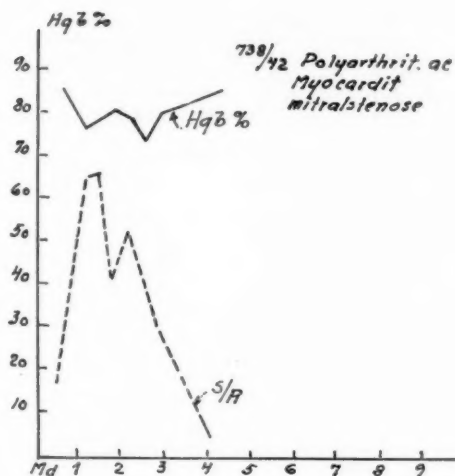


Diagram 10.

choreic myocarditis — in accordance with its more benign nature — there was definitely less tendency to anaemia (diagram 11).

The Sedimentation Rate (S. R.) in polyarthrit. has, as expected, shown considerably high figures. Simultaneous registration of Sedimentation Rate and hemoglobine reveals the characteristic crossing of the curves (diagram 13). This crossing sometimes occurs in the active phase, because the hemoglobine percentage rises quicker than Sedimentation Rate falls. If a slight myocardic affection occurs during the course of an acute polyarthrit. it is followed by a clear, but often slightly pronounced increase of S. R. (diagram 10). As the hemoglobine value in such cases is normal, no crossing of the curves will take place. In the «early» endocarditis the increase is often seen simultaneous with or just before the gallop rhythm is registrated. An increase can in this way be useful in the diagnosis of an imminent endocarditic process, as both stethoscopic and roentgenologic examinations may be negative.

The sedimentation rate in chorea is usually described as much lower. As I have here mainly treated the initial phase, a comparison is made between the sedimentation rate in the initial stage

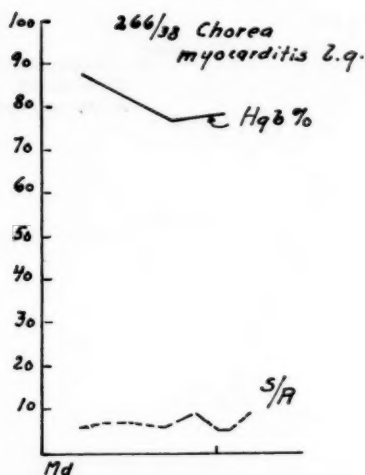


Diagram 11.

of chorea (without joint complic.), chorea + polyarthrititis and polyarthrititis (without chorea). The choreic disturbances have, as a rule, been in progress for some time before admittance. Consequently the values often refer to a more advanced stage. That is to say: Only chorea observed from the very beginning can be compared with polyarthrititis as to the sedimentation values. I have therefore compared the S. R. figures within the first 4 weeks after the appearance of the choreic symptoms with the figures in resp. chorea + polyarthrititis and polyarthrititis during the same period. (Table XII.)

The S. R. in chorea is normal or only slightly increased (40 of 48 between 0 and 10 mm). In chorea + polyarthrititis only 4 of 53 are less than 10 mm. In polyarthrititis (without chorea) only 5 (of 197) values are found to be under 10 mm. That is to say: While S. R. in chorea during the first 4 weeks is low, the »complicated» chorea during the same period presents a picture similar to polyarthrititis, although the increase is considerably more moderate. The majority of the higher values (50 mm and more) in the latter group were stated when the chorea appeared se-

Table XII.

S. R. (mm.)	Chorea (24 cases)	Chorea+poly- arthritis (28 cases)	Polyarthritis (50 cases)
0—10	40 tests	4 tests	5 tests
10—20	7 »	15 »	16 »
20—30	1 »	12 »	20 »
30—50	0 »	7 »	39 »
50—100	0 »	9 »	72 »
>100	0 »	6 »	45 »
	48 tests	53 tests	197 tests

Total tests: 298

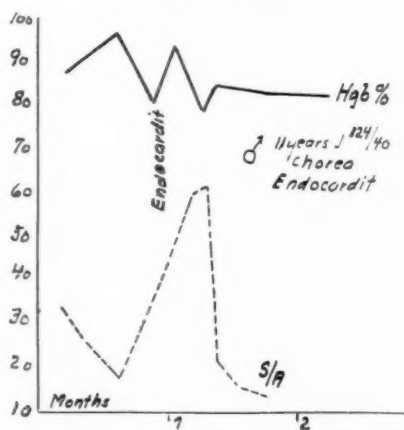


Diagram 12.

condarily to the polyarthritis. In *choreic myocarditis* a slight — if any — increase is noticed. The hemoglobine value is hardly affected (see diagram 11). In *choreic endocarditis*, however, a considerable increase in S. R. is mostly observed (not seldom without the corresponding decrease in hemoglobine) (diagram 12).

Finally it may be added that the number of leucocytes in the initial stage have been normal or slightly increased. In 94 cases of acute polyarthritis the following figures were found:

Number of leucocytes per cmm	Cases
5—10 000	51
10—15 000	27
15—20 000	10
20 000	6

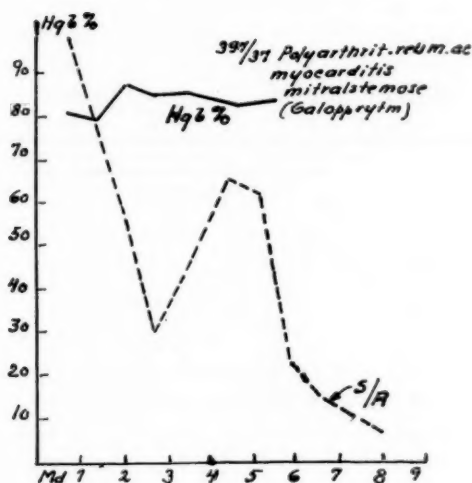


Diagram 13.

WHITLEY and BRITTON (29) mention, particularly in chorea, a marked *eosinophilia* (up to 10 %) in the active phase. Other authors (FRIEDMANN, HOLTZ (6)) only state eosinophilia in re-convalescence. In this material neither polyarthrit. nor chorea have shown definite signs of eosinophilia in the initial stage or later.

#### Conclusions.

Cardiac involvement was found in 91 % (76 of 83 cases). In 22 cases systolic and diastolic murmurs were stated by Fkg. (Thereof 9 by Fkg alone.) Gallop rhythm was demonstrated in 19 cases. (Thereof 12 by Fkg alone.) Ekg-changes were stated

in 72 (of 83). (Total cardiac percentage 58.) It is shown that chorea accompanied by joint symptoms considerably increase the percentage of heart complications. — In 20 % carditis was acquired during the first choreic attack. The corresponding figure in polyarthritis was 72 %. The difference in the figures seems to be due to the lesser frequency of choreic carditis. Heart involvement in chorea was found to be of a more benign character. Mortality (i. e. the number of children, who died in hospital) was 4.5 %. Recurrence percentage in polyarthritis was 23, in chorea 42 (total 31 %). Previous rheumatic infection in the family as to polyarthritis: 25 % (chorea: 7 %).

Initial tonsillitis was present in 46 % of the polyarthritis cases (in chorea: 7 %). Chronic inflammatory changes in the tonsils were stated in about 10 %. All the cases (21) of chronic tonsillitis were found in the group of children, in which the rheumatic infection started as an acute tonsillitis. The importance of the so-called »free interval» is pointed out. Tonsillectomy was performed on 46 children (10.3 %). It is stressed, that all the cases were later attacked by some kind of rheumatic disease. (Thereof 10 in direct connection with the operation.)

Abdominal pain as prevalent initial symptom was present in 9.4 %. — The importance of considering a rheum. inf. in every case of obscure abdominal pain in childhood is emphasized. Monarticular appearance was found in about 17 %.

Erythema annulare was only diagnosed in 9 cases (3.4 %), multiform erythema and rheum. nodules both in 1 %. — It is shown that E. a. and multiform erythema suggest a serious prognosis.

Anaemia was present in 30 % of the polyarthritis and 11 % of the choreic cases. A serious anaemia was especially observed in pancarditis and septic endocarditis.

A comparison is made between the S. R. in the initial stage of chorea, chorea + polyarthritis and polyarthritis (without chorea). —

Some details as to hemoglobine value and sedimentation rate in polyarthritis and chorea are described and discussed. In chorea S. R. is normal or slightly increased. In chorea + polyarthritis



the increase in S. R. is similar to polyarthritis, although considerable more moderate.

The hemoglobine value in chorea is — as a rule — normal. In choreic carditis (or polyarthritis) the tendency to anaemia is increased. The benign character of the three sound gallop is affirmed by the course of the hemoglobine and sedimentation curves.

### Summary.

A material is presented comprising 446 children treated during the period 1914—43 in *Kronprinsessan Lovisa's Children's Hospital* in Stockholm for acute rheumatic infection. (Polyarthritis rheum.: 248 cases, Chorea rheum.: 198 cases.)

*Ekg* and *Fkg* were systematically performed on 83 children during 1933—43. Age, year division, family disposition, mortality and recurrence percentage are investigated. Certain characteristic symptoms in the initial stage (abdominal pain, tonsillitis, free interval and monarticular appearance) are described. —

The results of *tonsillectomy* are discussed.

The frequency, diagnostic and prognostic value of erythema annulare, multiform erythema, rheumatic nodules and rheum. erythema nodosum are mentioned. Concerning the involvement of the heart, attention is drawn to the »primary» carditis, and the importance of *Fkg* for the early diagnosis of endocarditis is stressed (particularly phonocardiographic registration of gallop rhythm, systolic and diastolic murmurs are emphasized). The value of *Fkg* in the differential diagnosis between cong. heart disease, rheumatic carditis and »physiological» murmurs are discussed. —

Some details as to rheumatic anaemia and the sedimentation rate during the course of ac. e. rheum. inf. are demonstrated.

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## Über D-Vitamingehalt der Renntiermilch.

Von

GÖRAN GEZELIUS.

Verf. hat 1939 in Acta Pædiatrica einen Aufsatz über Rachitis bei Kindern nomadisierender Lappen veröffentlicht und darin das gehäufte Vorkommen von Rachitis-Fällen mit klinischen Symptomen bei Kindern von schwedischen nomadisierenden Lappen beschrieben. Dass Rachitis bei Lappenkindern vorkam, ist schon früher in Finnland und Norwegen (YLPPÖ, KLOSTER) konstatiert worden. In Schweden bestand dahingegen gemeinhin die Auffassung, dass Lappenkinder sehr selten rachitische Symptome hatten (SCHENK). Ich ging nun von der Annahme aus, dass die Lappen früher Zugang zu einer D-Vitaminquelle gehabt hätten, die sie jetzt nicht mehr anwenden, und dass diese Quelle die Renntiermilch gewesen sei, die durch ihren Fettgehalt (nach YLPPÖ enthält sie 18 % Fett) reich an D-Vitamin sein könnte.

Die Lappen haben durch ihre veränderte Lebensweise in den letzten Jahrzehnten allmählich damit aufgehört, Renntiermilch in grösserer Menge aufzuheben. Heutzutage nehmen sie Ziegen zu den Sommerwohnplätzen mit und wenden Ziegenmilch im Sommer und Herbst an. Im Winter wählen die Lappen ihren Wohnplatz so, dass sie Kuhmilch für die Kinder kaufen können. — Früher hatten die Lappen diese Möglichkeit nicht, sondern sie waren gezwungen, die Renntiermilch sorgfältig aufzuheben. Im Sommer und eine zeitlang in den Herbst hinein hatten sie frische Renntiermilch. In den anderen Jahreszeiten mussten sie konservierte Milch anwenden. Trotz der primitiven Lebensweise haben die Lappen 2 Methoden gehabt, um Renntiermilch für die Zeit, in der die Renntierkühe keine Milch geben, aufzubewahren: entweder stellen

sie eine Art Trockenmilch aus der Renntiermilch her, oder die Milch wird eingefroren. Das Eintrocknen geschieht so, dass die dickflüssige Milch in Renntierdärme gefüllt und im Rauchfang im Lappzelt aufgehängt wird. Auf diese Weise bekommt man die Renntiermilch in schmalen Stangen, die leicht auf den Umzügen mitgeführt werden können. Im Herbst, wenn es kalt geworden ist, wird die Renntiermilch eingefroren und kann so den ganzen Winter über aufbewahrt werden.

Tabelle 1.

Biologische Vitamin-D-Bestimmung (ausgeführt nach der kurativen Methode-Röntgen).

Ratte Nr.	Grad der Rachitis b. Beginn d. Ver- suches	Versuch	Tages- dosis	Heilungs- grad nach 10 Tagen	Mittelwert des Heilungs- grades
20 765	2+	Gefrorene Renntiermilch	2 g	4+	2 g gefrorene Renntiermilch = 5,18+
20 766	2+	» »	»	6+	
20 768	2+	» »	»	6+	
20 699	3+	» »	»	4+	
20 767	2+	Vitamin D Standard	1 I. E.	4+	
20 769	2+	» » »	»	3+	1 I. E. vitamin D = 4,67+
20 771	2+	» » »	»	7+	
20 772	2+	Neg. Kontrolle. Unbe- strahltes Erdnussöl (Arachidöl)	0,1 cc	0	
21 028	2+	Gefrorene Renntiermilch	2 g	2+	Die Tiere gehören demselben Wurf an.
21 029	3+	» »	»	7+	
21 031	2+	» »	»	5+	
21 026	3+	Vitamin D Standard	1 I. E.	tot	
21 027	3+	» » »	»	6+	
21 030	2+	Neg. Kontrolle. Unbe- strahltes Erdnussöl (Arachidöl)	0,1 cc	0	Die Tiere gehören demselben Wurf an.
21 039	4+	Gefrorene Renntiermilch	2 g	7+	
21 037	4+	Vitamin D Standard	1 I. E.	4+	
21 038	2+	» » »	»	4+	
21 036	2+	Neg. Kontrolle. Unbe- strahltes Erdnussöl (Arachidöl)	0,1 cc	0	

Dank Herrn Prof. HANS VON EULER's Entgegenkommen wurden die Untersuchungen über den D-Vitamingehalt der Renntiermilch im Biochemischen Institut der Hochschule in Stockholm ausgeführt. Die Tabellen stellen das Resultat dieser Untersuchungen dar.

Die Prüfung der eingefrorenen Renntiermilch zeigt also, dass ihr D-Vitamingehalt gross ist. Er entspricht ungefähr dem in der Kuhbutter im Sommer.

Tabelle 2.

Biologische Vitamin-D-Bestimmung (ausgeführt nach der kurativen Methode-Röntgen).

Ratte Nr.	Grad der Rachitis b. Beginn d. Versuches	Versuch	Tagesdosis	Heilungsgrad nach 10 Tagen	Mittelwert des Heilungsgrades
21 180	3+	Gefrorene Renntiermilch	0,5 g	0	
21 181	3+	»	»	1+	
21 182	2+	»	»	0	
21 187	2+	»	»	0	
21 184	2+	Vitamin D Standard	1 I. E.	6+	
21 185	2+	»	»	2+	
21 186	2+	»	»	5+	
21 183	2+	Neg. Kontrolle. Unbestrahltes Erdnussöl (Arachidöl)	0.1 cc	0	
			Die Tiere gehören demselben Wurf an.		

Die Tiere konnten nur mit grosser Schwierigkeit dazu gebracht werden, die Probe zu essen.

Versuch mit grösseren Gaben scheint folglich nicht durchführbar zu sein.

### Zusammenfassung.

Verf. vertritt die Ansicht, dass die fettreiche Renntiermilch eine D-Vitaminquelle für die Lappen darstellte, und dass sie diese früher gewissenhafter ausnutzten. Untersuchung der Renntiermilch auf ihren D-Vitamingehalt hat gezeigt, dass sie ungefähr ebensoviel D-Vitamin enthält wie Kuhbutter im Sommer.

### Summary.

The author has assumed that the Lapps, in their reindeer milk which is so rich in fat, have had access to a source of D-vitamines which they have hitherto most carefully utilized. Tests of reindeer milk, in respect to its percentage of D-vitamines, have shown, too, that it contains about as great a percentage of D-vitamines as cow's milk in the summer.

### Résumé.

L'auteur a supposé que les Lapons ont trouvé dans le lait de renne, riche en graisse, une source de vitamines D dont ils ont auparavant tiré profit avec plus de soin. L'examen du lait de renne quant à sa teneur en vitamines D a aussi prouvé que ce lait contient à peu près autant de vitamines D que le beurre de vache en été.

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FROM THE PEDIATRIC CLINIC OF KAROLINSKA INSTITUTET AT KRON-  
PRINSESSAN LOVISA'S CHILDREN'S HOSPITAL, STOCKHOLM.  
HEAD: PROFESSOR A. LICHTENSTEIN.

## **Electro-Encephalographic Examinations of Imbeciles.**

### **Regarding the alpha frequency in spastics and mongoloid idiots.**

By

**SIV GUNNARSON.**

In investigations regarding the relation of the electro-encephalogram (eeg) to the development of the brain, interest has been concentrated especially on the occurrence and frequency of alpha waves.

The alpha waves, which were first described by BERGER (1924) in man, are normally large regular waves, which usually have a frequency of 10 per second, and are best recorded in leads from the occipital lobe. No alpha waves can be recorded during the first two months of life and, when they do appear, they are sparse and somewhat irregular during the first few years, not attaining a frequency of 10 per second until the age of ten (BERGER 1932, DAVIS and DAVIS 1936, DURUP and FESSARD 1936, LOOMIS and collaborators 1936). LINDSLEY in 1936 made a systematic study of this question and, in a material of some 100 children, found an increase of the alpha wave frequency from about 4 per second at the age of four months up to 11 per second at the age of ten to eleven, followed by a fall to an average of 10.4 per second in adults.

BERNHARD and SKOGLUND (1939), in a material of 177 children and 23 adults, showed that the increase of the alpha wave frequency from year to year during the age of childhood follows a logarithmic curve.

BERGER (1931) examined 10 adult mentally defectives and found that their alpha frequency lay below the normal value

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for normal adults. RAHM and WILLIAMS (1938) confirmed this finding in a material of 35 mentally defectives. KREEZER in 1939 had collected a material of altogether 130 mentally defectives, including 50 mongoloids. He found a certain correlation between the mental age and the electro-encephalogram in patients affected with hereditary mental deficiency and in mongoloids, namely a statistically significant correlation between the mental age and the amplitude of the alpha waves as well as between the mental age and the alpha index (*i.e.* the percentage of alpha waves relatively to other waves at a given length of the eeg). He also found that at a low mental age the alpha frequency was likewise low, being about 5 waves per second. The alpha frequency did not fall parallel with the mental age: it dropped suddenly at a mental age of about 5 years or under. Below that mental age he found sparse regular frequencies of the alpha type, a smaller wave amplitude and a lower frequency of regular waves than in children of normal intelligence. He stated, however, that the electro-encephalogram could not be used for diagnostic purposes in imbeciles, as there are marked variations in every individual.

BERNHARD and SKOGLUND (1939), in a study on a minor scale, showed that the alpha frequency of imbeciles was in most cases low, as compared with that of normally intelligent children of the same age. Only 4 out of 12 imbeciles examined had an alpha frequency within normal values, whereas that of the others was considerably below the values for normally intelligent children of the same age.

Investigations have also been made in cases of acquired mental deterioration, such as dementia connected with acquired myxedema, general paralysis, or alcoholism as well as in dementia senilis: in cases of high-grade dementia it has been found that the alpha waves were sparse or had vanished, being replaced by long irregular waves with a frequency of 2—3 per second (GUILLAIN 1939). GIBBS (1942) contends that high-grade dementia may occur without corresponding changes in the electro-encephalogram, and that there is no parallelism between the encephalogram and mental disorders. Slow waves may occur alike in a person



of high intellectual standard and in an imbecile who has not learnt either how to eat or talk.

The genesis of the alpha waves has also been discussed. KREEZER (1936) supposes that the reduced frequency of regular alpha waves in imbeciles may be due to defects in the organic connection between large groups of cells. BERNHARD and SKOGLUND (1943), after studies on children of different ages in regard to the blocking of the alpha rhythm of the brain potentials on irritation with light, showed that the blocking time was a function of the duration of the alpha waves; and that the blocking time was reduced during the age of growth in direct proportion to the shortening of the duration of the alpha waves and their increasing frequency. This reduction was observed also in a case of imbecility, where the duration of the blocking by irritation with light was in direct proportion to the duration of the alpha waves. These investigators therefore consider that the alpha wave frequency may be an expression of the velocity in central processes of hitherto unknown nature.

#### *Own investigation.*

The object of the present investigation was to study whether any difference in alpha frequency could be shown in two different groups of imbeciles, namely in mongoloids, whose mental backwardness is due to a constitutional brain defect, and in spastic subjects whose mental development has been retarded by a cerebral hemorrhage during delivery.

*Apparatus:* The apparatus used was a four-stage condenser-coupled amplifier with 2 push-pull initial stages. The effect was recorded on one beam of a cathode ray oscillograph, and on the second beam of the tube exact time determination was arranged by condenser shots with intervals of  $\frac{1}{10}$  second. The electrodes consisted of small silver discs 9 mm in diameter and about  $\frac{1}{4}$  mm in thickness. Monopolar record was used. The use of several leads was considered superfluous, the intention being only to reckon the alpha frequency. The active electrode was placed over the occipital region in the median line, after the hair had been shaved at a place about the size of a penny and the fat in the scalp had been removed with benzene. Under the silver electrode some ointment was placed as a conducting medium to the skin, and the electrode

was fixed with collodium. The indifferent electrode was fixed in the same way on the right mastoid process. The electrodes were held in place by a rubber band round the head.

During the experiment the subject was placed on a bed in a sound-proof, electrically shielded room, and was ordered to lie relaxed in the dark with open eyes. Care was taken to avoid drowsiness and sleep, conditions which are known to influence the alpha-rhythm (DAVIS and collaborators 1938).

The material consists of 42 imbeciles from asylums in the environs of Stockholm, 20 of them being typical mongoloids and 22 spastic. In all cases the spasticity was believed to have been acquired by injury during delivery. Intelligence tests were made on all of them according to the method of TERMAN-MERRILL. In cases where the patient could not cope with some

Table 1.  
Mongolian idiots.

Case	Chronological age	Mental age	I. Q.	$\alpha$ /sec.	Normal variation (acc. to BERNHARD & SKOGLUND) $\alpha$ /sec.
1	5 $\frac{2}{12}$	<2	<30	6	7.5-9.2
2	6 $\frac{2}{12}$	<2	<30	6.5	7.5-9.2
3	9	2 $\frac{10}{12}$	29	5.5	7.5-10.2
4	13 $\frac{8}{12}$	<2	<30	5	8.3-11.0
5	15 $\frac{7}{12}$	3 $\frac{1}{12}$	21	6	8.2-11.1
6	16 $\frac{7}{12}$	4	25	6	8.2-11.1
7	17	3 $\frac{7}{12}$	22	5.5	8.2-11.1
8	17	4 $\frac{6}{12}$	28	6.5	8.2-11.1
9	19	2 $\frac{6}{12}$	16	6	9.0-11.0
10	20	4	27	5.5	9.0-11.0
11	46	4 $\frac{7}{12}$	29	10	9.0-11.0
Doubtful cases.					
1	9		59	4-5	7.5-10.2
2	11 $\frac{1}{12}$	4 $\frac{2}{12}$	38	5-6	8.4-10.4
3	18 $\frac{2}{12}$	2 $\frac{2}{12}$	17	6-7?	8.2-11.1
4	56	3 $\frac{11}{12}$	25	5?	9.0-11.0

Table 2.  
Spastic subjects.

Case	Chronological age	Mental age	I. Q.	$\alpha$ /sec.	Normal variation (acc. to BERNHARD & SKOGLUND) $\alpha$ /sec.
1	5 $\frac{2}{12}$	<2	<30	8	7.5-9.2
2	5 $\frac{9}{12}$	2 $\frac{9}{12}$	47	7	7.5-9.2
3	7 $\frac{10}{12}$	4 $\frac{7}{12}$	58	8	7.5-10.3
4	8 $\frac{1}{12}$	<2	<30	7	7.5-10.3
5	8 $\frac{9}{12}$	<2	<30	7	7.5-10.3
6	8 $\frac{9}{12}$	<2	<30	7	7.5-10.3
7	13	5	38	9	8.8-11.0
8	15	<2	<14	8	8.2-11.1
9	20	3 $\frac{8}{12}$	23	11	9.0-11.0
10	37	2 $\frac{1}{12}$	13	7.5	9.0-11.0
Doubtful cases.					
1	6 $\frac{1}{12}$	3 $\frac{5}{12}$	56	7.5	7.5-9.2
2	8 $\frac{7}{12}$	<2	<30	7	7.5-10.3
3	15		59	7	8.2-11.1
4	15	2 $\frac{3}{12}$	14	11?	8.2-11.1

test for a two-year-old, the mental age was simply stated to be lower than 2 years, it being considered unnecessary to continue the testing with another method. All of them had a mental age of under 5 years, which for most of them corresponds to an intelligence quotient of under 30 (see Tables 1 and 2). In addition, 16 children of normal intelligence were examined for purpose of control. They were chosen at random among patients hospitalized for various physical diseases, though children with fever or with symptoms from the central nervous system were excluded.

*Results:* The alpha waves are intermittent and, as above stated, occur much more irregularly in imbeciles than in normal subjects. Moreover, the low-grade imbeciles in this material were very difficult to examine and could not be induced to lie still and

## Spastic subjects.

## Mongolian idiots.

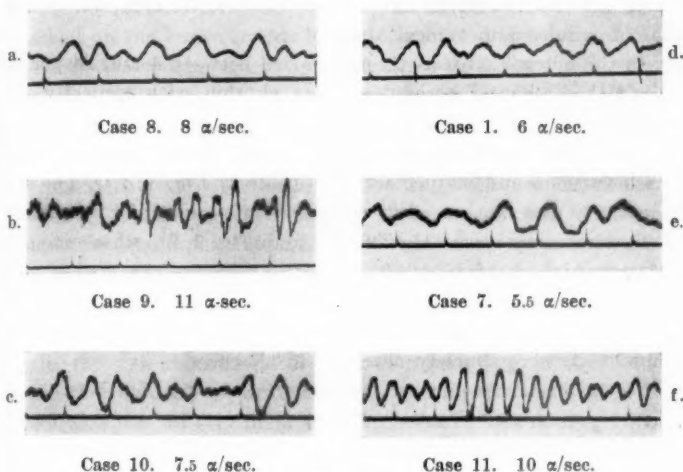


Fig. 1.

relax except for an extremely short time. The requirement as to the number of alpha waves in regular succession, therefore, could not be put as high as 10 (BERNHARD and SKOGLUND), but was reduced to 5. Muscular disturbances were frequently observed in the electro-encephalogram, especially in spastic subjects, but could be easily distinguished from regular alpha waves.

As regards the 20 mongoloids, whose age ranged between 5 and 56, no records could be taken in 5 cases, owing to their marked motorial unrest. In 4 cases, waves of the alpha type occurred so sparsely that 5 waves in succession could nowhere be reckoned. These waves are referred to below as »doubtful» alpha waves. The remaining 11 electro-encephalograms showed regular waves of alpha type, appearing 5 or more in succession.

As for the spastic subjects, whose age ranged between 5 and 40 years, 8 were so severely affected that they could not be induced to relax their cervical muscles. The muscular disturbances were therefore so dominant on the electro-encephalogram that no alpha rhythm could be reckoned. In 4 cases the alpha rhythm

was designated as doubtful when 5 regular waves in succession could not be recorded. The other 10 electro-encephalograms showed regular and typical alpha waves.

In the normal subjects the age varied between 4 and 24 years. All of them showed a regular alpha rhythm with typically recurring periods.

The alpha frequency in the mongoloids, in all cases but one, was between 5 and 6.5 per second (Table 1, Fig. 1 d, e, f). An exceptional case was an adult mongoloid with an alpha frequency of 10 per second (case 11, Table 1 and Fig. 1 f), whose mental age was highest of all ( $4\frac{7}{12}$  years). Among the 4 doubtful electro-encephalograms from mongoloids, long irregular waves of varying amplitude, with a frequency ranging between 4 and 6 per second, were sparsely observed in all cases.

The alpha frequency of the spastic subjects was between 7 and 11 per second (Table 2, Fig. 1 a, b, c). In the 4 doubtful electro-encephalograms from spastic subjects, periodically recurring regular waves with a frequency of 7—7.5 per second were sparsely recorded in 3 cases, whereas in one case irregular waves of 11 per second were observed.

All the normal cases showed an alpha frequency within normal limits of variation (Fig. 2).

Thus the alpha frequency in all the spastic subjects was higher than in the mongoloids (with a single exception, see above),

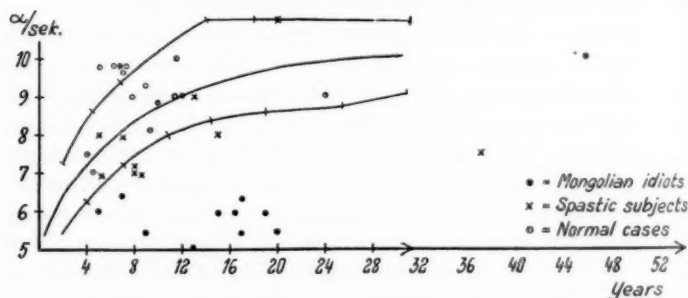


Fig. 2. The central line in the curve designates the average alpha frequency in individuals of normal intelligence of the respective ages, the upper and lower curves denote the normal limits of variation upwards and downwards.

as is graphically shown in Fig. 2. In this Figure the alpha frequency of the imbeciles as well as of the normal cases was marked on the curve traced by BERNHARD and SKOGLUND (1939), showing the continuous rise of the alpha frequency relatively to the age of life.

It has thus been found that the alpha frequency of the spastic subjects is not only higher than that of the mongoloids, but also in more than half the cases falls within the normal limits of variation for the age in question. True that among the spastic subjects whose alpha frequency falls within the normal limits of variation, we find the three cases which showed the highest intelligence quotients (cases 2, 3 and 7); but also cases with a very low intelligence quotient show an alpha frequency within, or in the neighbourhood of, normal values, *e.g.* case 8 with a quotient of 14 and an alpha frequency of 8 per second (Fig. 1 a) and case 9 with an intelligence quotient of 23 and an alpha frequency of 11 per second (Fig. 1 b). See Table 2 and Fig. 2.

Though the cases are few in number, the technical difficulties in obtaining satisfactory electro-encephalograms for low-grade spastic subjects may permit the publication even of such a small material. The observed difference between the two groups examined seems to indicate that a dissimilarity actually exists between the course of the central processes in constitutionally defective imbeciles and those who are retarded in development. In regard to the nature of the central processes, it is as yet too early to express an opinion.

### Summary.

42 imbeciles (20 mongoloids and 22 spastic subjects) were examined with electro-encephalograms. Regular alpha frequency was recorded in 11 mongoloids and 10 spastic subjects, irregular and sparse alpha waves in 4 mongoloids and 4 spastic subjects.

The alpha waves appeared more sporadically and in shorter periods in the spastic subjects and mongoloids as compared with the normal cases. In all cases of regular alpha frequency, a lower frequency was found in the mongoloids than in the spastic

subjects, with a single exception. The results in the cases with alpha-like, irregular waves correspond with the typical cases.

The alpha frequency in all the mongoloids with a low intelligence quotient was far below the normal values for the age, whereas the alpha frequency in all the spastic subjects, even in those with a very low intelligence quotient, fell within, or in the neighbourhood of, the normal limits of variation for the age.

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## **The Present Organization of School Hygiene in Sweden.**

By

**G. W. HERLITZ.**

Senior school medical officer,  
Member of the Royal Supervisory Board of Education.

Since 1944 school hygiene in Sweden is regulated after uniform principles. The direction of school hygiene is conducted by the central school authorities, the Royal Supervisory Board of Education, and the leader of the work is since the 1st of january 1943 the senior school medical officer, who is a member of the before mentioned board of education. In the charge of the Royal Supervisory Board of Education are both elementary and secondary schools with a total number of about 800 000 pupils.

For the hygiene work in the schools are appointed school physicians assisted by school nurses. Their work is chiefly preventive, while the medical treatment is attended to by other institutions. As a matter of course, a distinct line between prevention and treatment of disease cannot be drawn. The medical treatment in the schools, however, is confined to occasional prescriptions, which can be made without too much waste of time in cases, where the physician does not expect a continual need of treatment. Naturally, the school gives, as far as practible, occasional preparatory treatment in cases of sudden illness and accident. The school physicians and the school nurses are not allowed to make professional calls to the homes for medical treatment of the pupils.

A central task for the school is to teach the pupils sanitary habits, and to this aim school physicians, teachers and school nurses cooperate with the homes of the children.



Each pupil is thoroughly examined about every other year at the general class examinations. Examinations are also made of new-enrolled pupils. Besides these general class examinations that comprise all the pupils of a class, examinations are in case of need made of the so-called control children. As control children are regarded such children, as suffer from a chronic malady or run the risk of catching contagious disease in their environment. In the secondary schools the physician has to visit the school once a week during the course of the school-year to examine these control children. In the elementary schools such weekly examinations are prescribed for the great schools and for the schools, where full time nurses are appointed. In small elementary schools control examinations take place to such an extent as the school physician proves necessary. In this way a continual supervision of all the pupils is achieved.

The result of the examination is recorded uniformly for the whole country on a specially prescribed health card. This card accompanies each pupil from school to school, and from elementary school to secondary school. When the pupils have definitely left school, the cards are kept in a central record department in order to be accessible for scientific work. The health card, properly filled in, contains sufficient statements to satisfy the minimum claims laid to the examinations. The physicians are at liberty to keep supplementary cards. The health card comprises among other things questionnaires to the homes concerning previous diseases etc. Further, it contains statements about vaccinations and medical advice concerning choice of profession, which the physician is bound to give the pupils who are in want thereof, plans of the general class examinations, about attendance at gymnastics and at vacation colonies etc.

At the end of the school year the school physicians have to hand in annual reports about their work to the country medical head officers, to the local school authorities and to the Supervisory Board of Education.

A few details may here be pointed out.

All pupils have to be regularly examined by tuberculin, and those who react negatively are recommended to Calmette vaccina-

tion. The teachers are also under a certain control as regards tuberculosis.

At the age of 13 or 14 all the pupils have their colour sense tested, which is necessary considering the fact that about 20 000 or 5 per cent of all the boys in the schools have defective colour sense.

The organization of the school hygiene work of 1944 prescribes compulsory obligation for the teachers to send all the pupils who show psychical peculiarities to the school physician. As such cases are regarded also the pupils who have some difficulty in following the lessons. When such a pupil has been sent to the school physician or if he has attracted the notice of the school physician or the nurse, the parents the school physician and the teachers should work together in making a plan of suitable treatment. In different places of the country central offices for psychical advice are established under the direction of specially qualified physicians and pedagogues, with whom the schools can cooperate in these questions. In Sweden we soon hope to get a system of public offices for psychical advice, which stretches all over the country. This is a measure of great importance for the educational work.

In the secondary schools and the training colleges for elementary school teachers the school hygiene work is wholly paid for by the state. Accordingly, the fees of the school physicians and the salaries of the school nurses as well as the material they need for their work are wholly defrayed by public means. In the elementary schools one half of the physician's fee is paid by the state and one half by the commune. The same is the matter with the communal secondary schools, which get an additional grant from the state of 50 per cent to the salaries of the school nurses. In the elementary schools in the country the district nurses, who assist at the other hygiene and medical work of the place, generally serve as school nurses. One nurse has to superintend 1 500 school children at most.

In certain great secondary and elementary schools school nurses are appointed for full time service. In small schools the nurses are on duty only during certain hours of the week, and

besides they have full time work during a few weeks at the beginning of the school year, when the general class examinations take place.

The senior school medical officer is a state official with full time service. In some of the large cities (Stockholm, Gothenburg, Malmö) chief school physicians wholly paid by communal means are appointed for full time service. The other school physicians, who have part-time service, are allowed to hold other positions and to have practice of their own besides their work in the schools. The number of school physicians in the whole country will in a year probably amount to about 900, as the new organization of school hygiene of 1944 grows to its full extent.

The school hygiene work is an important link in the cooperation between school and home. The parents' interest for this important social medical work is stimulated by speeches and health hours in the schools and in many other ways. The school nurses visit in cases of need the homes of the pupils in order to give advice in health questions and to get necessary information about the pupils. This work of the nurses unites school and home in common work for the young people's health.

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## **What is the Cause of Harrison's Groove in Rickety Infants?**

By

**GILLIS HERLITZ.**

The characteristic rickety deformity of the chest, well known under the name of Harrison's groove has in general been understood to be the effect of the strain of the diaphragm at its attachment on the soft thorax wall. Closer inspection however shows that this conception can hardly hold good, but that there must be other causes of the phenomenon.

First of all it is obvious that the attachment of the diaphragm is not to be found on those places of the thorax where Harrison's groove lies. As I have been able to observe in a number of infants and school children, the latter of whom still retained remainders of the groove, the latter has, in an upright position, an almost purely horizontal course, emanating from the base of proc. xiphoideus and reaching approximately the anterior axillar line, where it becomes shallower and gradually vanishes. In so far as it is a question of the thorax, the diaphragm certainly projects from several ribs, but in a running line which, practically speaking, follows the edge of the aperture of the thorax the whole way to the base of proc. xiphoideus. Above this line no attachment for the diaphragm on the ribs is to be found. In corpses one can thus pass the hand along the inner side of the thorax wall as far down as to the lower aperture, where the diaphragm offers resistance. The matter is best elucidated by the illustration (Fig I). The picture depicts the situation in an adult — in infants the thorax is more bell-formed and angulus epigastr. somewhat shallower —, but it can also serve to illustrate the situation in

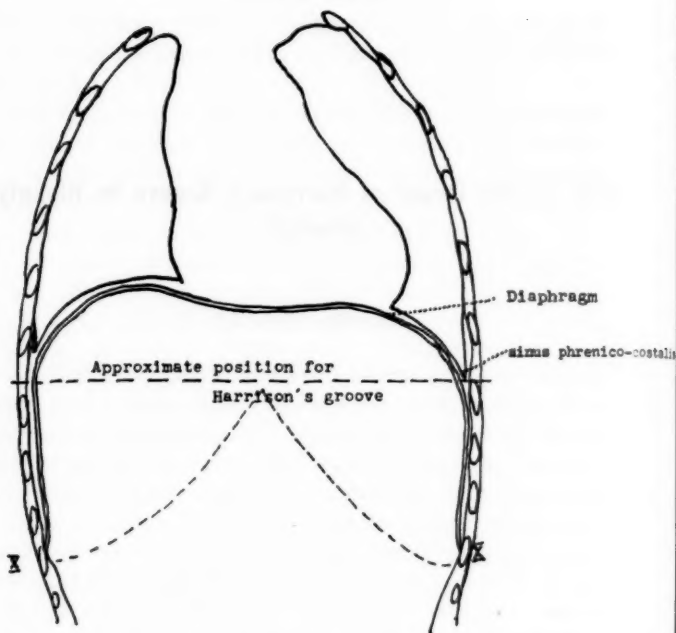


Fig. I. Frontal section through the thorax of an adult, somewhat in front of the middle axillar line. According to PERNKOPF: *Topogr. Anat. des Menschen*, Berlin 1937.

children. The approximate position for Harrison's groove is drawn on the figure. Under such circumstances it is unthinkable that it is a strain on the attachment of the diaphragm which is the cause of Harrison's groove.

What effect then has a contraction of the diaphragm on the chest walls? Inasmuch as the diaphragm runs a fair distance upwards along the inner side of the thorax before diverging inwards to the median line, it is obvious that the strain which the diaphragm, when contracting, exercises on the thorax at the place of its attachment, ensues in an almost kephal direction. The space between the thorax wall and that part of the diaphragm close to the thorax is a vacuum; this in conjunction with the

circumstance that the uppermost part of the abdominal cavity is filled with massive organs, prevents the lower part of the diaphragm that adjoins the thorax, from leaving the thorax wall. The effect of the diaphragm at the place of its attachment is thus primarily a raising of the thorax; this raising of the thorax is also made possible during the contraction of the diaphragm through the resistance offered by the large organs of the abdomen when the vaults of the diaphragm descend.

If the thorax is lifted below, then the lower ribs must, by reason of the construction of the joints of the ribs, for purely mechanical reasons, swing outwards — upwards. The effect of this is that the lower aperture of the thorax is expanded. The large abdominal organs must also have the same effect when they try to give way to the pressure from the vaults of the diaphragm which are sinking. The result of diaphragm contraction is thus not only a raising of the lower ribs which appears to be quite inconsiderable, but also a rather considerable expansion of the lower sections of the thorax. Owing to the normal effect of the diaphragm, this expansion of the thorax has, of course, only influence within the lowest parts of the thorax, mainly indeed in those situated below the turning point where the diaphragm leaves the thorax wall. Above this line which, practically speaking, coincides with sinus phrenico-costalis the retractive force of the lung acts on the thorax wall constantly. With this, one of the conditions is also provided to which Harrison's groove owes its origin: a bend outwards below the mentioned line conditioned by the action of the diaphragm and surely in no small degree either, by the volume of the abdominal organ — as well as a retraction above the line conditioned by the elasticity of the lung. One must bear in mind that the groove is almost always easier to demarcate in the downward direction, where the wall of the chest diverges sharper outwards, than is the case in the upward direction where the limits are more shifting and even with strongly pronounced groove are often difficult to fix. Sometimes it is indeed less a question of a groove than of a bend in the thorax wall.

If one radiographs a child with Harrison's groove, it will be

seen that, if the child breathes quietly, the position of the groove is practically on the same altitude as that of sinus phrenicocostalis. Now sinus is not fixed but moves up and down with the breathing, neither is Harrison's groove so sharply marked but in fact rather shallow. One might say that the bottom of the groove viz. the middle line in the longitudinal direction of the groove is on the same level as sinus in quiet breathing. In four infants of 8—12 months of age and in three other children of 1—3½ years of age I have marked the middle line of the groove with pieces of lead and then radiographed the children whereby the above results were obtained. If children scream, the diaphragm sinks appreciably and the groove sometimes appears to lie on a level with the tips of the vaults of the diaphragm, but as mentioned before, with quiet breathing the conditions are different.

One particular force which operates at about the same spot of the thorax wall, viz. at the sinus phrenico-costalis, Professor LAURELL<sup>1</sup> has drawn my attention to. When the diaphragm contracts, a strain must ensue on the thorax wall just at that place where the diaphragm turns from where it lies close to the thorax wall in order to proceed inwards towards the middle line of the body. This strain owes its existence to the fact that the power of adhesion prevents the diaphragm from leaving the thorax wall. I obtained an interesting proof of the accuracy of this in the Infants' Ward at the Maternity Department where I was occupied with other matters for some time. It often happened there, particularly after meals, that children began hiccuping violently. Hiccups are considered as pure diaphragm cramp and there were opportunities there to study the effect of the jerky contractions of the diaphragm on the soft chests of the new born. If the stomach was fairly well filled, it could be perceived that each time, the jerky retraction of the chest wall occurred at about the place and to the same length that Harrison's groove has in older children. When the stomach was empty this retraction occurred farther down, sometimes one could even see that the edge of the

<sup>1</sup> I should like here to extend my sincere thanks to Prof. HUGO LAURELL, X-ray Department, Academical Hospital, Uppsala, for all the help rendered me and all the interest in my investigations.

aperture of the thorax was drawn in with the hiccups. Once I succeeded in radiographing the child before the hiccups ceased, in this case there was no doubt that the jerky retractions occurred just at the position for sinus phrenico-costalis.

As a result of these observations it will hardly be too bold to assume that Harrison's groove is mainly the result of a combined effect on the wall of the chest of normal diaphragmatic action and the retractive force of the lung. The effect of the diaphragm does not here take the form of a strain on the attachment of the diaphragm, but consists in a strain on the thorax wall at the place of sinus phrenico-costalis. Moreover the diaphragm produces effect by expanding the lower sections of the thorax; this expansion is however to a certain degree surely, dependent on the volume of the abdominal organs.

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## **Instruction in Social Pediatrics.**

By

**URBAN HJÄRNE.**

As Docent in pediatrics at Upsala University the author was faced in 1932 with the task of lecturing on appropriate pediatric themes to students of medicine at the time that they were completing their clinical service and attending clinical lectures on pediatrics. I had already then got experience from several children's hospitals of the difficulty of succeeding in detail in imbuing the students with more than a very superficial orientation over many of the practical pediatric problems which present themselves to the practising doctor and the practising specialist. Instruction at the clinics had naturally to be so planned that the students learnt at first hand the physiology of the individual child, the conditions of development and the purely physiological, medical goals for an optimal development. Further the instruction embraced the system of examination of the healthy and ailing child, and a thorough survey of the diseases of children. In this connection the important part played by the child's surroundings was of course always stressed, the importance of measures affording assistance to mothers and children, the possibility of extending relief to parents, and of instructing mothers. But for natural reasons all measures and all instruction concerned the problems of individual children as they arose in the reception hall or at the sick bed.

With the introduction of the Child Welfare Act of 1924, it was provided that in any district where a commune- or State-employed doctor resided he should become a member of the Child Welfare Committee. Even then Child Welfare Committee activities

often demanded a medical attitude towards the problem. Many of the social-medical measures which were in discussion during the 1930's, and which by degrees were ordained by the Parliament, multiplied the work of the Child Welfare Committees. Thereby their need of medical knowledge was increased. And it was often desirable that the doctor was conversant with child and juvenile somatic and psychic problems. This applied for instance to such questions as economic relief in cases of pregnancy or confinement, and aid to mothers; further the supervision of children where difficulties of upbringing or adaptability existed.

During the 1930's the number of child welfare centres funded on private initiative increased, and the Parliament decreed in 1937 that maternity centres should be established over the whole country to allow the possibility of medical control for all mothers during the period of pregnancy and to afford medical supervision and control of all children under school age. Primarily medical attention was compulsory only for public secondary schools. Some of the larger towns however organised the examination and supervision of their schoolchildren on their own initiative — a medical supervision which in certain cases was also arranged in schools in rural areas. It was the great desire of children's doctors that this medical control of schoolchildren should embrace all schoolchildren in the whole kingdom; an aim which was realized by a decree of the Parliament in 1944. During the decade of 1930 one of the most burning questions was the growth of the population in Sweden in view of the catastrophically declining natality. The study of this problem touched often purely medical questions, and the propositions resulting from the discussions had purely medical aims and desires.

There was therefore every reason to presume that in their coming activities the future doctors would concern themselves with social-medical, social-pediatric problems. However it was unfortunately so that the purely clinical and polyclinical instruction had only too often to be limited to the individual child. Hospital instruction, with ailing children as objects of study, did not always offer the necessary contact with the problems which arose in the community. The future doctors were not always

conversant with the child welfare organizations of the community and their methods, or with the possibilities of aiding and instructing parents which the community offered. Despite this a large part of the doctor corps would in the future participate in social-hygienic work among children.

I was therefore faced with the pressing necessity of imbuing those who were studying pediatrics with an orientation over these problems. In their future activities as doctors employed by the province or commune, as hospital doctors, general practitioners, school doctors or specialists in pediatrics, they would in all probability partake in this work.

Medical and social work among pregnant mothers and among children and juveniles demands an exact knowledge of the normal development at these ages; of the physiology and pathology at these stages. It demands an exact and minute knowledge of the conditions for optimal development; of the factors which are necessary for, and which further the development. It demands an exact and minute knowledge of conceivable disorders, of detrimental factors and their effect. This applies both to the physical and mental development. This knowledge is a necessary stipulation for successful therapeutic activity. The treatment of the sick without investigating the nature of the ailment is quackery which can be greatly injurious to the patient. Social-medical activity without knowledge of the conditions for an individual optimal development during childhood years is a not less dangerous social quackery.

The lecture courses were directed by me according to the following plan:

As an introduction: A survey of the distribution of the population according to different age-groups, followed by a detailed study of the growth of the population. A relatively thorough study of this vital question was made. The decline in natality is a general European problem, as was illustrated by statistics and diagrams. The significance of the decline in natality on the labour and unemployment questions in various occupational groups was illustrated — on the agricultural and foodstuffs industries, on housing production

and all its collaborating enterprises, on the clothing industry, on schools and educational institutions, on all free professions. Of particular significance is the fact that the decrease in the number of potential parents must automatically lead to a further decrease in the number of children in the future. It was shown how the pending decrease in able-bodied persons decreases the number of taxpayers, and thereby the State income, how the declining number of recruits jeopardized the country's defensive strength. It was shown how a depopulated country with large natural resources must always exercise a strong power of attraction over over-populated neighbouring countries with a large surplus birth-rate. Many of the reasons which are presumed to contribute towards a decline in the birth-rate have a hygienic component. Many of the suggestions for remedial measures for increasing the birth-rate which arose during discussions in Sweden were of a pronounced medical-pediatric character. Among others they included the question of economic relief to families possessing many children; rent subvention. The importance of the dwelling question must be stressed. One suggestion concerned the health control and health care of mothers, children and juveniles.

Like all other members of society doctors must naturally form an opinion on all social-political propositions involving remedial measures, based on a knowledge of the actual conditions and of the effects of the methods proposed.

#### *Study of Mortality and its Causes.*

For natural reasons during the clinical study of ailments the standpoints applicable to the individual patient take the foreground. The question of health and illness is treated primarily as a problem in the fight between the infections or deterioration in health which affect the individual patient and the resistance which he has, or which can be imparted to him. In this respect great attention is naturally paid to the patient's normal surroundings. It is however extremely important that the students are not only given a knowledge of purely medical, bacteriological, biological-immunity, therapeutical problems. One must enable them to visualize how failures of health, ailment, infections, arise

during the various ages, stages and seasons, in various social and economic classes in the country and in the towns, in various occupational groups, in various parts of the country, among children in and out of wedlock. This study must be based largely on a scrutinization of mortality and its causes:

In this exposition I was guided by the following main points:

*General Mortality in Sweden:*

The course of the mortality curve from 1751 up to now.

Mortality in the various age groups from 1751 up to now.

*Infant Mortality:*

Definition. The different registrations of »babies born alive». The border between »miscarriage» and »baby» from a statistical viewpoint. Infant mortality in different countries.

*Infant Mortality in Sweden:*

Infant mortality in towns and in rural areas.

Infant mortality in and out of wedlock.

Infant mortality during the various months of the first year of life.

Early mortality, causes and counteraction.

The distribution of different ailments and causes of mortality during babyhood and infancy under the headings:

diseases in early infancy

infection illnesses

respiratory organ illnesses

gastric and intestine illnesses

»other illnesses» (rachitis, convulsions, spasmophilia, accidents, etc.).

Distribution of the above groups according to various ages and various seasons.

Infant mortality according to various methods of rearing.

Infant mortality according to mother's age and condition of health.

Infant mortality according to size of family.

Infant mortality according to different intervals between confinements.

Infant mortality according to mature or immature delivery.

Infant mortality according to social conditions.

Infant mortality graded according to dwellings, to fathers annual income, whether the mother is employed outside the home.

In this connection a short survey of the economic conditions and dwelling conditions in Sweden. Finally the importance of a knowledge of child welfare, which renders it possible largely to counteract the deteriorative factors.

It was shown how the mechanism of every cause can be supposed to operate; for every and all of the factors it was discussed how the resistance forces might be diminished or the risk increased. Above all the means of evading the deteriorative factors were indicated; prophylactic in the individual case, and prophylactic in general; the various social-medical, social-hygienic and other measures. The problem was often reduced to a question of instruction and control; doctors' and nurses' responsibility of assuring that the experience and demands of Science, based on biological and clinical research, are applied practically to all children. Every error of upbringing, nursing and care which is met with should above all give the responsible doctor an impulse to improve the instruction, enlarge the public's knowledge, and organise a more efficient control of the application of knowledge within the field of his activity. Further one can appropriately discuss the reasons of the decline in infant mortality and point out where, under what circumstances and in what way further improvements can be attained. The most essential measures of the moment may be considered to be those relating to child welfare centres, the organisation and activities of which should be surveyed. This should preferably take place in conjunction with practical service at child welfare centres. A large number of doctors will of course, in their future careers, work at child welfare centres, and it is therefore of extreme importance that they acquire a routine during their years of study, learn all the details of their field of activity, without necessarily being trained specialists.

In connection with pregnancy or delivery, there may be a particularly great economic strain on the families or mothers.

This economic pressure may force the mothers to undertake heavy work shortly after confinement. This may prevent visits to doctors for health control, it may prevent the mother from following the hygienic instructions she receives. The poor economy can hinder her from obtaining during the pregnancy and nursing period a diet which is satisfactory from a nutritive and physiological viewpoint. She is forced to undertake all work in the household and for the rest of the family — shopping, cooking, washing-up, cleaning, washing, tending the garden and farm-yard in rural areas, apart from rearing the infant. This can increase the risk of miscarriage during pregnancy, immature birth or other complications. During the period of nursing, when the mother needs a nutritive diet and the chance of rest and sleep, the economic strain can detract from the mother's possibilities of regaining her strength, and lessen the chances of breast-feeding. When a woman »for reasons of pregnancy or confinement is in obvious need of relief» she may receive Mothers' Assistance, i. e. she may obtain goods at the expense of the State, receive aid, or, in certain circumstances, cash up to a value of Kr. 400:—. She may be given relief for the purpose of bettering the diet, for board and lodging, for domestic help, help with the washing, for bed equipment, for her own shoes and clothes, if necessary. A considerable portion is devoted to dental treatment. The Child Welfare Committees must examine the application for Mothers' Assistance, and furthermore are responsible for seeing that the means placed at the disposal of the recipient are most suitably employed. Where mothers have received Mothers' Assistance the children should stand under the control of the child welfare centres. The doctor has a major part to play in all this, and therefore great attention should be paid to it in the study of social pediatrics.

As far as infants are concerned it is often desirable from a social standpoint that they should be taken care of during those hours of the day in which the mother works. From an educational viewpoint it is often desirable that the child should associate with comrades and coevals. The main medical problems during these ages are the risks of infection, which increase in proportion to the number of children assembled in the groups. The current desire



is that all organizations for the care of children during a certain part of the day should have access to a doctor to control the children's health and reduce the hygienic risks as far as possible. The future doctors must therefore be taught both the need of this care of children and of the most suitable measures for diminishing risks.

Since the Parliament decree of 1944 medical supervision in the schools has been widely extended. The possibility now exists of employing school doctors and school nurses in all school districts, for all schools in towns and rural areas. One can calculate that when the activity is fully developed at least 800 of Sweden's doctors will be engaged with school health to some degree. They must therefore be equipped to fulfil their obligation in this respect. As the details of this work have already been treated in C. W. Herlitz' article, I need only mention the main points which should be known to a future doctor. I am presuming that their clinical studies have made them familiar with the physical and psychical development of childhood years — with the general tendencies of normal development and its great field of variation. Further, I pre-suppose that they have learnt the characteristics of normal growth and that they have gained an impression of the psychical structure and tendencies of different children, of deviations in talents, of the influence of detrimental effect of surroundings, and of the various methods of treatment which are advisable for different children. Apart from the purely medical measures desirable in the cases of many of the children they and their parents must be educated to sound habits of life in general. Among other things this involves seeing that their daily routine allows appropriate time for work and for rest, appropriate time for out-door exercise, appropriate time, place and composition of diet. Dentistry must be applied, the importance of organizing school baths in some form. The doctor should make himself familiar with the medical considerations in respect of vocational advice. Every doctor in his daily work comes often into contact with children who live in circumstances of a deteriorative hygienic or social nature, deteriorative circumstances which can lead to serious disorders.



They may be cases of parental neglect or bad upbringing in a physical respect, it may be an inability to give the children satisfactory supervision and upbringing. The doctors who work in schools and in Child Welfare Committees should themselves know well how evil social conditions foster medical risks; should know how the effects of harmful surroundings induce deviations from normal behaviour. Above all he should know this to enable him to suggest prophylactic remedies of a suitable nature.

According to the present study plan the course in pediatrics covers a period of 3 months. My experience in the instruction of social-pediatrics during the years 1932—1942 at Upsala University is that one can cope with the programme outlined above in about 20 lectures, each of one hour. Any great curtailment of this time is not suitable. On the other hand it would be extremely valuable and more stimulating for the listeners if they were personally given certain short tasks within the sphere, which can afterwards be the subject of discussion between the teacher and the participants in the term instruction. They would thus attain a more vivid personal knowledge of literature, of statistical works in this sphere. It should be possible to enable them to follow the activities of child welfare centres, and of school doctors and nurses. It would be extremely valuable for them to scrutinize the documentary side of the Child Welfare Committees' activities in reviewing cases registered for supervision, review the dependants at children's homes, etc. It would be of great significance for the students if they were enabled to participate in the reviewing of and treatment of Mothers' Assistance cases. All this would animate the problem for them during their studies. And when, as qualified doctors, they are called upon to form an opinion on these problems they will have some personal experience and routine to fall back upon.

The clinical examination and its results is decisive for the diagnosis and therapy in the case of individual sickness. The statistical investigations into the standard of living and health in the different groups of the population are equally indispensable in the social-medical, social-hygienic spheres. A com-

ination of scientific pediatric knowledge and vital statistics such as Fr. Th. Berg possessed is the best guarantee that both the doctor's personal work and civic obligation to improve the standard of living for the community in general is fulfilled in the best possible manner. Place must be made for both directions of study in the tuition of pediatrics.

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## **The Syndroma Hypoglycemia-Hydrops-Erythroblastemia in New-born.**

By

**SVEN JOACHIMSSON.**

The spontaneous hypoglycemic symptom complex has been known since a couple of years after the discovery of insulin; not until insulin had been introduced into therapy, however, did hypoglycemia and its clinical symptom become familiar, at first only as a result of overdosing with insulin, but later also as a spontaneous phenomenon (HARRIS, 1924). Subsequently an abundant literature has grown up round this symptom complex, and comprehensive casuistics have contributed towards the shaping of the morbid picture and to the pathogenesis, which naturally enough has attracted great interest. The majority of cases which have hitherto been described have been those of adults, and in most of these it has been possible to prove — at autopsies or operations — organ changes as the cause of the hypoglycemic condition: tumour or hyperplasia of the insular elements of the pancreas, hypofunction of glands with counter-insular effect and liver injuries of various kinds — to mention generally the causes which are most important in principle. There are also functionally conditioned hypoglycemiae e.g. such as are seen after excessive physical exertion, with exhaustion of the body's glycogen reserves as the immediate cause. There are examples of insulin symptoms after ordinary physical exertion, a disturbance in balance in the adrenalin-insulin system having been assumed. Persons with a labile blood sugar regulation may develop symptoms of hypoglycemia after a meal abundant in carbohydrates, as a result of a great post-hyperglycemic hypoglycemia.

Spontaneous hypoglycemia is met with in children also, but in them the functionally conditioned cases appear to predominate, in contradistinction to the state of things among adults. RECTOR and JENNINGS (1937) collocated the child cases which had been described in the literature up to that time. According to this collocation, it is in the first place children in the ages of infancy that are affected by the disease; it is unusual under one year, and the first attack seldom appears after the age of 3 years. Of 35 cases no organic factor could be proved in 32, in 2 cases there was hyperinsulinism, and in one case a fatty liver with a liver insufficiency. In the authors' material of 11 children it was impossible to prove organic changes to explain the morbid picture, possibly with the exception of one case. Here in Sweden MALMBERG and WAHLGREN (1936) described a case of a 7-year-old girl with pluriglandular insufficiency, and WENDT (1940) gave an account of 4 cases of purely functionally conditioned spontaneous hypoglycemia.

In the majority of cases of functionally conditioned hypoglycemia in children, starvation was indicated as the cause (RECTOR and JENNINGS), and in that connection support has been found in the fact that in children starvation relatively rapidly leads to exhaustion of the body's glycogen reserve, and that the growing undeveloped organism lacks the capacity to maintain a normal blood sugar by means of sufficiently rapid glycogenesis (RUMPF, 1924). In cases of gastro-intestinal disturbances convulsions with acetonemia and hypoglycemia have been seen, which are considered to be due to a defective regulation of the insulin production (FANCONI, 1934). The younger the organism, the more defective would be the blood sugar regulation, and a support for this is the circumstance that in these children the spontaneous hypoglycemic attacks disappear with increasing age.

With these statements as a starting-point, the pre-requisites for the new-born to exhibit spontaneous hypoglycemic conditions should be great. For the new-born infant — which must be said to be an immature individual — it is necessary to accommodate itself to the conditions of extra-uterine life, which at first are unfavourable from the point of view of carbohydrates. Often a child

has to begin life with 24 hours' starvation, and even during the immediately following days it is not infrequently in a state of relative starvation, as the amounts of nourishment supplied during that period are small. To judge from the mention of them in the literature, however, spontaneous hypoglycemic conditions during the new-born period appear to be very rare, apart from the case of infants of diabetic mothers, for whom, of course, conditions are special. On the other hand it has long been known that a certain *hypoglycemia* is present during the new-born period. GREENVALD and PENNEL (1930) investigated the blood sugar in 94 healthy new-born infants between the ages of 0—10 days. During the first 24 hours of life they found a mean value of 0.071 %, with 0.062 and 0.083 as the lowest and highest values respectively; during the following three days the mean value was 0.074 (0.06—0.094), and the blood sugar remained on about that level for the remainder of the investigation period, with a slowly rising tendency. SEDGEWICK and SIEGLER (1920) and LUCAS (1921) obtained similar values. HARTMAN and JAUDON (1937) found that values below 0.05 % were not unusual and even noted, in otherwise completely healthy children, values below 0.03 during the first three days of life. KETTERINGHAM and AUSTIN (1938), who investigated the blood sugar in new-born children during the first three days of life, registered the following values: immediately after birth 0.103 %, after 3—6 hours 0.067 (0.057—0.079), during the second 24 hours 0.07 % (0.052—0.103), and during the third 24 hours 0.076 % (0.057—0.110). Still lower values were found by MILLER and ROSS (1940): in full-term children a mean value of 0.049, with a minimum value of 0.042, and in premature infants a value of 0.038. VAN CREVELD also found very low values for premature infants, the lowest being 0.03 %. Of course the results of these blood sugar investigations in the new-born vary appreciably, which will probably be due to the methods. Thus MILLER and ROSS and HARTMAN and JAUDON, who found surprisingly low values, had eliminated all other reducing substances in the blood, except the glucose, before titration. This is considered to lead to a mean difference of 0.027 %, and if this is taken into consideration, their values agree with those of GREENVALD and PENNEL. I myself have

followed, during a week, the blood sugar in 5 new-born infants and found values tallying with those of the latter authors.

Thus it appears to be established that there is a certain hypoglycemia during the »new-born period»; also that such low values are not infrequently observed that clinical symptoms might be expected, but, as has been pointed out above, this seems to be very rare. On the subject of hypoglycemia during the »new-born period» some authors have, however, given expression to opinions which may be worth quoting. MILLER and ROSS consider the absence of hypoglycemic symptoms in the new-born to indicate »that the new-born infants, in general, adjust themselves without difficulty to low concentrations of blood sugar». HARTMAN and JAUDON give an account of 15 cases of children of diabetic mothers and make a comparison between the blood sugar in new-born infants of healthy and diabetic mothers. They point out that the blood sugar conditions in these two groups are similar on the whole: a very marked tendency towards low blood sugar values during the first 2 days of life. The authors state, however, that the children of diabetic mothers have a very much more pronounced tendency to clinical manifestations of their hypoglycemia, but continue: »the frequent occurrence in normal new-born infants of cyanosis, irritability, listlessness and muscular disorders, such as hypotonicity, hypertonicity and twitchings might very well be due sometimes to hypoglycemia, which is almost a normal occurrence during the first few days of life». However, they do not describe any actual cases of hypoglycemic symptoms in new-born infants.

On the other hand, HIGGONS (1935) describes a case of convulsions in a new-born child where no other explanation of the convulsions than a low blood sugar value (0.05 %) could be proved. Higgons suggests that, in every case of unexplained convulsions in new-born infants, the blood sugar should be determined to eliminate the possibility of diagnostic mistakes — usually hemorrhagia intracranialis.

RECTOR and JENNINGS (1937) publish a similar case: a 3-day-old boy with convulsions, apathy, spasticity and a blood-sugar value of 0.036 %. The convulsions were alleviated with an intravenous supply of glucose. At the age of 3 months, however, the

child was obviously under-developed, and an encephalogram revealed atrophy of the brain, so that the possibility of an intracranial hemorrhage cannot be excluded in this case. The authors themselves consider that a state of starvation was the cause, and the favourable effect of the supply of glucose will most probably argue in favour effect of the convulsions having been hypoglycemic.

The most frequently observed and best known morbid condition in new-born infants which has been set in connection with hypoglycemia is, however, that met with in the infants of diabetic mothers. During the first few days of life they may exhibit the picture of a typical hypoglycemia with convulsions, hypertonia and hypotonia, as well as general restlessness; and apathy and unwillingness to take food are often stated to be characteristic. However, the most pronounced symptom in these infants is attacks of cyanosis of a more or less serious nature, and not infrequently these attacks are followed by extremely serious disturbances in circulation with collapse, which often leads rapidly to death. With these conditions very low blood sugar values have been proved many times, but such is far from always the case — almost equally often they are normal. On the other hand, severe hypoglycemia may be noted in diabetic mothers' children who are quite free of symptoms. In autopsy cases, an indubitable hyperplasia of the insular elements of the pancreas are often found, i.e. a morphological expression of hyperinsulinism. Owing to the discrepancy between the clinical symptoms and the blood sugar values, however, this condition in the infants of diabetic mothers is not considered to be due to an isolated hypoglycemia, but a more general disturbance in hormonal balance, in the first place in the insulin-adrenalin-system, has been assumed (SÖDERLING, 1940).

During last year in the Children's Department at Borås Hospital some cases of hypoglycemia with clinical symptoms in new-born infants of *healthy* mothers were observed. As, apart from the hypoglycemia, these cases exhibited other symptoms which are particularly interesting for the ethiology, I give an account of them below.

*Case I.*

Case no. 728/43. Girl, birth weight 3700 gr, normal partus. Mother healthy bipara. 9-year-old sister healthy. Nothing of interest hereditarily, no diabetes known in the family. The child cried and had a good colour immediately after birth, and during the first 12 hours of life. About 12 hours after birth a couple of attacks of cyanosis which soon passed off, but as they recurred the child was transferred to the Children's Department. From the status: typical hydropic child with pronounced hydrops especially in the face, so that it »squelches». Hoarse cry. On admission to the department very cyanotic and rather cold — temp. 35°, C. Cries and kicks strongly when skin is stimulated and then her colour becomes better. Respiration somewhat shallow and irregular. Muscle tonus without any definite remark. Lungs and heart without remark. Liver and spleen not palpable, no resistance in the abdomen. Circumference of skull 35 cm, no tension of fontanelles. During the next few days she had several attacks of cyanosis, was apathetic, sucked poorly and had to be fed with a sound. On the fourth day of life an attack of convulsions was observed, with twitchings in the left leg and right arm and in the face. There was no explanation of the convulsions. On the fifth day, however, 2 blood sugar determinations were made, with the following result (fasting values): 0.044 % and 0.108 %. It was now suspected that this was a case of a hypoglycemic condition, so that renewed examinations were made: 2 fasting values on the 7th day of life showed persisting and now more extreme hypoglycemia: 0.026 % and 0.025 %. On the 9th day continous blood sugar examinations were made during 24 hours, controls being made on the 15th and 18th days. The values are given in table I, and, as is shown by the figures, there was still an obvious hypoglycemia on the occasion of the last examination. On the 21st and 24th days of life, when adrenalin experiments were made and glucose loading effected, the fasting values were normal for the age, but the reaction of the blood sugar to the adrenalin and glucose respectively indicate a persisting disturbance in the blood sugar regulation. (Table II.) The temperature was normal the whole time without any extra supply of warmth, except on the day of admission. The blood picture exhibited nothing remarkable except a relatively large number of erythroblasts: on the 3rd day of life 2940 nucleus-bearing red blood corpuscles per mm<sup>3</sup> (0.05 %) on the 5th day of life 102/mm<sup>3</sup>. No anemia and no icterus. Owing to the fact that a certain hydrops and erythroblastemia were thus present, a determination of the blood group was made in respect of Rh with the following result (Dr Birger Broman):

The child A MN rh-

The mother A<sub>1</sub> MN rh-

Thus the mothers pregnancy had not been heterospecific in respect of Rh and no anti-Rh-agglutinins could be proved.



Table I.

## Case I. 24 hours blood sugar values.

At 8 days of age.	%	At 15 days of age.	%
At 11 o'clock . . . . .	0.047	At 12 o'clock . . . . .	0.100
13 » . . . . .	0.046	14 » . . . . .	0.099
15 » . . . . .	0.058	16 » . . . . .	0.075
17 » . . . . .	0.082	18 » . . . . .	0.064
19 » . . . . .	0.051	20 » . . . . .	0.087
21 » . . . . .	0.074		
23 » . . . . .	0.074	At 18 days of age.	%
1 » . . . . .	0.085	At 0950 o'clock . . . . .	0.050
3 » . . . . .	0.066	1330 » . . . . .	0.055
5 » . . . . .	0.065	1730 » . . . . .	0.040
7 » . . . . .	0.072		
9 » . . . . .	0.047		

Table II.

## Case I. At 21 resp. 24 days of age.

## Blood sugar determinations after the administration of

0.2 cc adrenalin subcut.	%	8 gr glucose per os.	%
Fasting. . . . .	0.076	Fasting. . . . .	0.074
15 minutes after . . . . .	0.101	15 minutes after . . . . .	0.080
30 » » . . . . .	0.105	30 » » . . . . .	0.074
45 » » . . . . .	0.103	45 » » . . . . .	0.086
60 » » . . . . .	0.099	60 » » . . . . .	0.086
90 » » . . . . .	0.072	75 » » . . . . .	0.080
120 » » . . . . .	0.070	90 » » . . . . .	0.074
150 » » . . . . .	0.080	105 » » . . . . .	0.069
180 » » . . . . .	0.080	120 » » . . . . .	0.094
210 » » . . . . .	0.064	150 » » . . . . .	0.055
240 » » . . . . .	0.055	180 » » . . . . .	0.063

After the first attack of convulsions was observed on the 4th day of life the child had — with decreasing frequency — occasional slighter attacks of convulsions and attacks of cyanosis, the general condition improved gradually, she became livelier, ate better, the hydropic con-

dition disappeared entirely, and when she was discharged, at the age of 5 weeks, she was quite normal and weighed 3 840 gr.

At a control examination at the age of 11 months, the child was quite normally developed both physically and psychically and had not been ill in the meantime.

**Summary:** Without there having been any difficulties in partus, a new-born infant has attacks of cyanosis at the age of 24 hours, after a couple of days convulsions, the child is apathetic, eats badly. It is hydropic, has slight erythroblastemia, for the rest nothing remarkable in the status. The only possible explanation of the convulsions was that at repeated determinations a definitely pathologically low blood sugar value was established, which persisted till c. 3 weeks after birth, i. e. about as long as the attacks of the convulsions. The adrenalin and glucose loading curve show pathologically low blood sugar rise. The convulsions, attacks of cyanosis, and apathy persist in a decreasing degree for about 3 weeks, and gradually disappear at the same time as the blood sugar becomes normal, and the hydropic condition recedes. At the age of 5 weeks the patient is discharged healthy, and at the age of 11 months is quite normally developed.

#### Case II.

Case no. 721/43. Girl. Mother healthy, nothing of interest hereditarily, no diabetes in the family. Primipara. *Hydramnion*. Weight of the placenta 900 gr, for the rest nothing of interest at partus, which was at the normal term. The child's birth weight was 3 130 gr. At the age of 3 hours transferred to the Childrens' Department, owing to suspected hydrops universalis congenitus. On admission to the Department, the patient was cold — temp.  $36^{\circ}$  C. — cyanotic and somewhat limp, but improved greatly with alternating hot and cold baths and oxygen-gas. Extreme oedema all over the body, localized particularly in the back and under the chin, least pronounced on the arms. Deep marks after pressure. No signs of ascites or hydrothorax. On the lungs medium râles and reduced respiration sound. Heart without remark. Liver and spleen not palpable. During the first 24 hours slight attacks of cyanosis. On the 10th day of life the blood sugar was determined, with the following result: 2 fasting values of 0.016 % and 0.193 %. A 24-hour blood-sugar curve on the 12th day of life exhibited very large variations in the values but no markedly low values. (Table III.)

Erythroblastemia was proved in the blood: 6 800/mm<sup>3</sup> (0.15 %), 1 780, 840 and 42/mm<sup>3</sup> on the 1st, 2nd, 3rd and 4th days of life respectively,

Table III.

Case II. At 12 days of age 24 hours  
blood sugar values.

Time	Blood sugar	Time	Blood sugar
	%		%
11	0.120	23	0.155
13	0.066	1	0.083
15	0.125	3	0.188
17	0.084	5	0.085
19	0.152	7	0.125
21	0.086	9	0.101

a somewhat immature white blood corpuscles picture but no anemia, no icterus. On account of the combination erythroblastemia — hydrops, a severe form of familial erythroblastosis was suspected at first, and therefore a blood group determination in respect of Rh was made, with the following result (Dr Birger Broman):

The child O M rh-

The mother O MN rh-

No anti-Rh- or other irregular agglutinins could be proved in the mother's blood.

After a great fall in weight, which was to be expected in view of the hydropic condition (lowest weight 2 440 gr), and after the 3rd day of life when the cyanosis attacks had ceased, the child got on very well, ate well and increased in weight. Temp. normal the whole time. Discharged in good condition on the 20th day of life and has hitherto, 11 months after birth, developed normally, according to controls by the Infant Welfare Centre.

*Summary:* A 3-hour-old infant is transferred from the Maternity Department to the Children's Department on account of suspected hydrops universalis cong. The infant has severe hydrops confined to the skin, is cyanotic and apathetic and has a definitely pathological erythroblastemia. During the following 3 days slight attacks of cyanosis. On the 10th day, at intervals of a few hours, a very low and a strikingly high blood sugar value are established, both fasting values. The 24-hour blood-sugar curve on the 12th day of life exhibits considerable variations.

After the cyanosis attacks on the first days and a great loss of

weight satisfactory condition and development. Discharged in good condition on the 20th day. Normally developed at the age of 11 months.

### Case III.

Case no. 222/44. Mother healthy. Primipara. Partus without remark at the right time. Infant a boy, birth weight 3 290 gr. During the first 24 hours nothing of note as regards the child. On the 3rd day he was found with a bad colour and shaking all over his body, and he was therefore sent to the Children's Department. On admission there he was apathetic, reacted badly to pinching and pricking, strikingly pale but not cyanotic. Respiration without remark. He had attacks of rather violent tremors in the arms and legs, as in ague. Tonus somewhat increased. The skin slightly oedematous, but at the same time hard, as in scleroedema. Slight icterus. Lungs and heart without remark. The blood sugar was immediately determined and was 0.032 %; two hours later when the condition was unchanged 0.035 %. Subsequently 6 gr of glucose was administered per os for glucose loading, and 20 minutes later the tremors ceased and did not return. Unfortunately the glucose loading was unsuccessful owing to the use of wrong reagents, but it was repeated the next day, on the 4th day of life, and as a result gave a curve which, after a low starting value — 0.05 % — exhibited a somewhat slow but, from a quantitative point of view, normal rise. After 3 hours it still only showed a slight tendency to fall. (Table IV.) Six days after birth the blood sugar was still low — 0.059 %. The blood picture normal. No erythroblastemia, moderate icterus neonatorum.

Table IV.

Case III. At 4 days of age.

*Blood sugar determinations after the administration  
of 6 gr glucose.*

[illegible]

When the tremors had disappeared after glucose loading they did not recur. During the first few days the patient was apathetic and sucked

badly, but at the age of 8 days, when he was discharged, he sucked a teat well, cried and kicked strongly, the scleroedematous skin changes had receded. His development, controlled at the Infant Welfare Centre at the age of 6 months, has been normal during that period.

*Summary:* A previously quite normal, 3-day-old boy is found cyanotic and with tremors. The blood sugar, tested immediately, is 0.032 %, controlled after some hours 0.035 %. The condition is relieved with a supply of glucose. Glucose loading on the 4th day of life shows a slowly rising curve, and after 3 hours only a slowly falling tendency. Low blood sugar — 0.050 % — still 6 days after birth. After transitory apathy and poor suckings the patient is discharged in good condition at the age of 8 days. Normally developed at the age of 6 months.

*Case IV.*

Case no. 124/44. Mother healthy, bipara. Partus without remark, about 3 weeks later than expected. The infant, a boy, birth weight 5 330 gr. Owing to apathy and feeding difficulties, the child is transferred on 3rd day of life to the Children's Department. From the beginning the child was dark red and, when crying, bluish-red. From the status: *large dark red child*, flesh more than normally developed, firm turgor, polycythemic colour and slightly hydropic appearance, scleroedematous parts on both buttocks. Nothing of note from the internal organs. Liver and spleen not palpable. Navel without remark. No icterus.

The infant very apathetic the whole time and had to be fed with a sound. On the 5th day of life marked dyspnoea with a respiration frequency of 60/min. On the 6th day a rise in temp. and subsequently the child had a continuous 39—40° C, though no explanation for it could be found. On the 8th day the patient had a deep cyanosis attack and collapse. Alternating hot and cold baths, adrenalin and oxygen-gas improved his condition, and the child recovered its characteristic colour: dark red and slightly cyanotic. During the following days occasional cyanosis attacks, which were relieved in the same way as the first attack. By degrees loose râles from the lungs. The attacks of cyanosis were then accompanied by attacks of convulsions, and in one such attack the patient died on the 10th day of his life.

*Blood status:* on the 2nd day of life Hb 137 %, red blood corpuscles 6.67 mill. Erythroblasts: 25, 18, 10/200 white blood corpuscles on the 4th, 5th and 7th day respectively. The white blood corpuscle picture without remark. Owing to the hydropic condition and the erythroblastosis indicated, a blood group determination was made in respect of Rh, with the following result (Dr Birger Broman):

The child: B MN P+ Rh+

The mother: B M p- Rh+

Thus there are no indications for an iso-immunization of the mother, and in her blood serum no irregular agglutinins or more pronounced hemolysins are proved.

On account of the striking resemblance which the patient exhibited to the type of children that diabetic mothers are liable to give birth to, a blood sugar determination was made on the 3rd day: 0.031 % (fasting value). Glucose loading in the 4th day (Table V) gave a slowly rising curve, the maximum not being reached until after 2 hours, and after 3 hours the values were still high. A 24-hour curve on the 5th day of life showed normal conditions. An *adrenalin experiment* on the 9th day led to practically no increase in the blood sugar. However, the patient was then almost moribund with grave disturbances in circulation, so that there is a possibility that the adrenalin was not resorbed.

Table V.

Case IV. At 4 days of age.

Blood sugar determinations after the administration  
of 10 gr glucose. %

Fasting . . . . .	0.074
30 minutes after . . . . .	0.101
60   "   "   " . . . . .	0.124
90   "   "   " . . . . .	0.137
120   "   "   " . . . . .	0.139
150   "   "   " . . . . .	0.133
180   "   "   " . . . . .	0.132

*Autopsy:* An unusually large child for his age, with a c.  $\frac{1}{2}$  cm thick panniculus adiposus. In the internal organs in general extreme dilatation of the vessels, with small hemorrhages both in the parenchyma and subserously. No free intracranial hemorrhage, but here as elsewhere flaccid vessels, and here and there in the brain substance hemorrhages hardly the size of a pin's head. For the rest nothing remarkable macroscopically from the internal organs. In the back of the head an induration about the size of a half-penny in the subcutis, which when cut through, gave the impression of being conditioned by a necrosis.

*Microscopical examination* (Prof. Reuterwall):

The subcutaneous induration in the subcutis conditioned by an inflammatory process with diffuse necrosis and abundant lymphocytic infiltrates. No indications of pneumonia in the lung parenchyma. In the liver severe changes, localized in the first place in the porto-biliary

areas and adjacent parts of the liver lobuli with necrobiosis to necrosis, abundant plasmolymphocytic and leukocytic infiltrates. In the *brain* extreme hyperemia in the capillary vessels. No foci in the parenchyma. In the soft membranes hyperemia, in places hemorrhage, and in a number of places fairly abundant agglomerations of round cells mingled with leukocytes. *Pancreas* without particular remark. Well pronounced Langan's cell islands. In the kidneys moderate hyperemia, in the spleen, suprarenal capsules, thyroidea and hypophysis pronounced hyperemia of the capillaries, in places with small hemorrhages.

*P. A. D.* Hepatitis acuta + Inflammatory foci in subcutis + Leptomeningitis + Pronounced hemorrhagic diathesis.

Thus in all these four cases a *disturbance in the regulation of the blood sugar was proved*, firstly, by the pathologically low blood sugar values, even for their ages, secondly, in three of the cases, by a pathological course of the glucose loading curve. KETTERINGHAM (1940) made glucose loading curves after a supply of 1.75 gr. of glucose for 9 breast-fed and 6 formula-fed children between the ages of 5 and 10 days. In the breast-fed infants she found a mean maximal rise in the blood sugar of 0.06 % after  $\frac{1}{2}$  hour, in formula-fed infants the same rise after 1 hour, and in both groups the blood sugar was lower than the starting-value

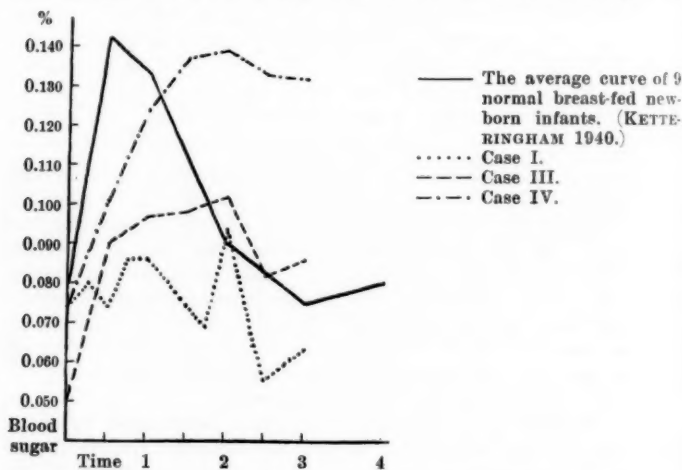


Fig. 1. Blood sugar curves, following the administration of glucose.

after 3 hours. Thus in comparison with the conditions in these healthy children, the curves we obtained in our cases were clearly pathological. This appears from fig. 1, where the curve for KETTERINGHAM's mean values is reproduced, and the curves from our cases have been drawn in.

All the four cases which have been described here had also clinical symptoms which could be set in connection with the hypoglycemia. Three of them had convulsions, all had attacks of cyanosis, and three of them were obviously apathetic, did not take the breast, were difficult to feed; and in the first three cases these symptoms were not explained by anything but the low blood sugar.

On the other hand, the fourth and last case is more debateable. In this case there was a septic condition with inflammatory changes, *inter alia* in the liver and meninges. The diffuse liver injury which was revealed at the autopsy, may very well have given rise to a hypoglycemia, and the convulsions, attacks of cyanosis, the infant's apathy and unwillingness to feed may be explained by the meningitis and the septic condition. On the other hand, even from the beginning, before any septic symptoms appeared, the child had an obvious »endocrinous» appearance, and there were apathy and feeding difficulties at that early stage, as well as disturbances in the blood sugar regulation. The erythroblastemia was most pronounced during the first few days and receded when the septic condition developed. It therefore appears probable to me that from the first the infant had an endocrinous disturbance, and that the morbid picture was subsequently complicated by a septic infection.

The clinical symptoms exhibited by our cases were such as are usually seen in cases of intracranial hemorrhage during the new-born period. The practical conclusion which can be drawn from the experience of these cases therefore appears to me to be an emphasis of HIGGON's statement quoted above, that more often than is now done as a rule, determinations should be made of the blood sugar in inexplicable cases of convulsions, cyanosis attacks, apathy and poor sucking in the new-born; such determinations could be of value, especially from the prognostic point of view.

Apart from disturbances in the blood sugar regulation and the clinical symptoms, which gave us the picture of a spontaneous hypoglycemic syndrom during the new-born period, these cases had some further symptoms which must be considered remarkable.



The first three cases were more or less *hydropic*, in one case there was *hydramnion*, and the fourth was an unusually large infant with slight hydrops, and an appearance for the rest strikingly that of the new-born infants of diabetic mothers. Finally, in three of the cases an *erythroblastemia* was proved, which must be considered pathologic. Two of them had 0.05 and 0.15 % erythroblasts respectively, and a third 25/200 white blood corpuscles on the third, first and third days of life respectively. ALZIZOGLU (1933) and LIPPMAN (1924) indicate 0.01 % as the normal border-line for the first day of life. The question naturally arises whether the simultaneous appearance in these cases of hypoglycemia, hydrops and erythroblastemia was a fortuitous coincidence, or whether they had any connection with each other.

In a discussion of the *etiology* in these cases of hypoglycemia, consideration must be paid to the hypoglycemia normally present in the new-born, which in the premature may be fairly considerable. With this as a starting point it would perhaps be most natural to explain our hypoglycemias as extreme variants of the physiological hypoglycemia during the new-born period, due to the debility, a deficient biological maturity. Nor are oedematous conditions of various kinds anything unusual in the new-born, and they make their appearance, especially in weakly children, as a sign of immaturity, as does also a certain erythroblastemia. Thus the presumed debility itself would afford an explanation of the hypoglycemia as well as the erythroblastemia and oedematous conditions. In view of the liver's central position in the metabolism of carbohydrates and its importance for the extra-medullary formation of blood, a poorly developed liver function suggests itself in the first place.

This explanation, a biological immaturity localized particularly in the liver, can surely not be entirely rejected, but other points of view as to the etiology are obtained if the morbid pictures in our cases are compared with conditions in the infants of diabetic mothers, where there is reason to assume that the cause of illness is a hormonal disturbance of some kind arising under the influence of the diabetic disturbance in the metabolism of the mother organism. In these mothers *hydramnion* is not infrequently met

with, in the infant hydrops is not unusual, and in the cases where the blood has been more thoroughly investigated, erythroblastemia has been proved significantly often; and at autopsies blood-forming foci in the liver. Thus SÖDERLING (1940) describes 3 cases, 2 of which are stated to be hydropic, in one of the cases hydramnion was present at partus. MILLER & ROSS (1940) describe 6 cases, 4 of which had erythroblastemia, a circumstance that these authors considered remarkable, and which was to be the subject of their further study, one of these cases had oedema of the leg. BAUER & ROYSTER (1939), who collocated 13 cases from the literature, mention in one case polyhydramnion, and in two cases, on which autopsies were performed, erythropoiesis in the liver. Apart from the hyperplasia of the Langerhans' islands in the pancreas occurring almost regularly, SMITH and OLNEY (1938) found in one case a very marked erythropoiesis in the liver, and in the circulating blood from various organs on an average 1 % of nucleated red blood corpuscles. Finally, mention will be made of case c: VI in VAHLQUIST's thesis (1941), an infant of a diabetic mother with a morbid picture which led to the diagnosis *icterus gravis non letalis*. At partus there was a considerable hydramnion, the infant had oedema of the leg and an erythroblastemia of 0.22 %.

The most pronounced condition of hydrops and erythroblastemia during the new-born period is of course that met with in connection with the so-called erythroblastosis, called by BROMAN (1944) *Morbus haemolyticus neonatorum*. In this connection it is worthy of note that in cases of typical familial hydrops universalis congenita and *icterus gravis*, autopsy reveals severe hyperplasia of the insular elements of the pancreas, and — even for the age — a definitely increased store of glycogen in the liver, heart and musculature of the skeleton. LIEBGOTT (1938) describes two such cases of hydrops congenitus of his own and post-examined Schridde's case from 1910, with the same result. BENECKE (1939) gives an account of 3 cases of *icterus gravis*, where examinations of the pancreas, liver, heart and musculature of the skeleton, showed the same picture.

These observations imply of course a morphological criterium of

a hyperinsulinism. If they are correct, it might be expected that hypoglycemia would also be found in case of morbus haemolyticus neonatorum. However, I have not succeeded in finding any particulars as to the state of the blood sugar in this morbid condition, and personally I have not yet had any opportunity to investigate it.

Thus, by way of *summary*, the following may be established: on the one hand there is a morbid picture in the new-born, with disturbances in the blood sugar balance leading to hypoglycemia, combined with hydramnion at partus, hydrops in the infant and erythroblastemia; on the other hand cases of familial erythroblastosis are described, in which morphological expressions of a similar disturbance in blood sugar regulation have been proved.

I will not draw any conclusions from this parallelism, my material being all too small and too incompletely investigated. So much may probably be assumed, however: that this similarity in the morbid pictures may in principal reflect a similarity as regards the cause of its appearance. The condition of the infants of diabetic mothers has been assumed to be due to a disturbance in the hormonal balance and the hormonal genesis appears to me to be the most probable in our cases also — perhaps a latent diabetes in the mother, although the blood sugar examinations on the mothers gave no support for it. With regard to the familial erythroblastosis, it is now known, of course, that they are a product of an antigen-antibody reaction; it has not yet been possible to explain satisfactorily how the antibodies then formed exercise their influence (BROMAN, 1944), but the placenta is of course an internal secretory organ which is not left unaffected in cases of morbus haemolyticus neonatorum (TSCHERNE, 1938); and dysfunction of the placenta may perhaps be conceived as giving rise to a hormonal disturbance in the foetus, with hyperinsulinism as the result, for which morphological criteria have been proved in some cases.

Thus, if the hormonal genesis is conceivable as regards the changes in the blood sugar substance, there still remain to be explained the disturbance in the fluid balance and the erythroblastemia. But greater light can only be thrown on these latter two

symptoms and on the blood sugar conditions by further clinical observations of the morbid conditions touched on here, and by further experimental investigations.

### Summary.

The pre-conditions for the appearance of hypoglycemia should be found in the new-born. There is, too, a certain physiological hypoglycemia during the first week of life, but it is seldom accompanied by clinical symptoms. An exception to this is provided by the infants of diabetic mothers, in whom special, hitherto unexplained, disturbances are present.

The author has observed 4 cases of hypoglycemia with clinical symptoms in infants of *healthy* mothers. Disturbances in blood sugar regulation were revealed, apart from the hypoglycemia, by means of glucose loading curves with abnormal courses. The clinical symptoms consisted of *convulsions* in 3 cases, *attacks of cyanosis* in all 4 cases, obvious *difficulties in feeding* in 3 cases.

The occurrence of these symptoms also in cases of intracranial hemorrhage is pointed out, and in that connection — when hemorrhagia intra cranialis is suspected on account of these symptoms but not verified — the importance is indicated of determining the blood sugar in order to avoid possible erroneous diagnosis.

In addition to the hypoglycemia with its clinical symptoms, some further symptoms of interest in these infants are pointed out: three of the infants were more or less *hydropic*, in one of the cases *hydramnion* was present at partus and in three of the cases a definitely pathological *erythroblastemia* was proved.

The author advances the suggestion that the whole of this morbid picture might be due to debility, a deficient biological maturity, in which, above all, a liver insufficiency is assumed to be the most important factor. The central position of the liver in the regulation of the blood sugar, its importance for the fluid metabolism and for the extra-medullary formation of blood, are pointed out as reasons why a biologically immature liver might give rise to this morbid picture.

However, other aspects of the etiology of the morbid picture in these cases are brought out by a comparison with the condition in the infants of diabetic mothers. According to the casuistics, the latter may exhibit exactly the same symptoms: hypoglycemia, attacks of cyanosis, convulsions, difficulties in feeding, hydrops, hydrops, erythroblastemia. On the other hand, in cases of typical familial erythroblastosis, hydrops universalis congenita and icterus gravis neonatorum, extreme hyperplasia of the insular elements of pancreas has been shown, as well as pathological stores of glycogen in different organs — a morphological expression of hyperinsulinism.

In view of the similarity between the symptom pictures in the cases described by the present author and those of the children of diabetic mothers, where a hormonal disturbance is considered to be present, the author's cases are also apprehended as being hormonally conditioned.

The blood sugar has been determined by the Hagedorn method and, in most cases, double determinations were made.

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FROM THE PEDIATRIC CLINIC OF KAROLINSKA INSTITUTET AT KRON-  
PRINSESSAN LOVISA'S CHILDREN'S HOSPITAL, STOCKHOLM.  
HEAD: PROFESSOR A. LICHTENSTEIN.

## **Massive Dose Prophylaxis with Vitamin D for Prematurely Born Infants.**

By

**TORSTEN JOHNSON.**

That prematurely born infants have a predisposition for rickets has long been known. MALMBERG (1939), in experiments with continuous vitamin D prophylaxis for premature infants, showed roentgenological rachitis in 14 of the controls who had not received the vitamin, whilst 7 went free; in several cases the disease was observable with the x-ray as early as one month after birth. On the other hand, those who had received a daily dose of vitamin D (2,700 international units) were relatively well protected, especially when, in 1941, he had increased the dosage to 10 000 units. This dose they had received since the end of the first week of life, in periods of 4—5 weeks with a fortnight's interval. Out of twenty-two of these cases, merely one developed an undoubted roentgenological rachitis, observable at the border of the costal cartilages, though not by the ordinary routine method with a roentgen photograph of the wrists or ankles. In a similar experimental series with a massive dose, STRÖM (1940) showed that a roentgenological rachitis developed in 13 out of 18 controls, whereas those who had received a prophylactic massive dose (100 000 international units of  $D_2$  per kg of body-weight) were entirely free from the disease during the first four months. At the age of six months, 2 out of 12 cases had developed roentgenological rachitis.

In examining the hospital records of 167 prematures who had been under the charge of the Gothenburg Child Welfare Centre

and who, as reported, had received about 1 500 units of  $D_3$  per day, ROOSWALL (1944) found in 5 cases a slight clinical rachitis, diagnosed on examination at some time between the age of 3—9 months. Whilst recognizing the value of the continuous prophylaxis thus adopted, he suggests, especially in view of Malmberg's investigations, that the dosage should be increased.

As will be seen from the above, recourse was had partly to continuous treatment, partly to a massive dose, in order to protect prematures against rickets. When a large single dose of vitamin D had first been tested successfully for the therapeutic treatment of rickets and spasmophilia (PETÉNYI, 1930, HARNAPP, 1935, SCHIRMER, 1937, GUNNARSON, 1939, and others) the massive dose began to be used also for the prevention of rickets. Besides Ström's above-mentioned series of experiments, similar investigations have been reported from foreign countries. WINDORFER (1938) made an experiment with a massive dose of 6—7 mg  $D_2$  per os to 32 prematures. More than half of these children (19) escaped the disease, whereas 7 developed a slight rachitis with softness along the cranial sutures and a blurred epyphyseal line on the ulna, and the remaining 6 a distinct rachitis with craniotabes and a frayed ulnar epyphysis. Believing this dosage to be too small he considered that it should be repeated after the lapse of three months. In a later publication (1940) he compared the result of the massive dose prophylaxy (10 mg  $D_3$ ) with that of continuous vigantol treatment (3 dr  $\times$  2) to prematures from the age of 6 weeks. He found the former method very superior, especially in view of the uncertain medication in the continuous treatment. For twins he found a greater need of D vitamin than for other prematures. TÜRK (1940), after giving a massive dose of 5—10 mg  $D_2$  per os, found no roentgenological rachitis during an observation period of nine months; on the other hand, in JUTTA BÜREN's (1942) experimental series of 69 cases, in spite of a massive dose of 15 mg  $D_2$  or  $D_3$ , partly per os, partly intramuscular, after about half a year merely two-thirds were free from rachitis. The best results were attained with 15 mg  $D_2$  per os and 15 mg  $D_3$  i.m. She considers that this dosage gives protection for 4—5 months.



All the authors seem to be agreed as to the value of the massive dose prophylaxis, although the results vary considerably. Factors such as subjective judgments, feeding, weight at birth, season of the year, etc., must, of course, be taken into account.

At the beginning of the nineteen-thirties, D<sub>2</sub>, the vegetable product obtained by the irradiation of ergosterin, was prepared in a pure form (WINDAUS and associates 1931—1932, ASKEW, BRUCE, CALLOW etc., 1931). Some years later D<sub>3</sub>, which can be derived from dehydrocholesterin and is of animal origin, was isolated. D<sub>2</sub> and D<sub>3</sub> have the same anti-rachitic effect on rats, whereas on chickens D<sub>3</sub> has a considerably stronger effect than D<sub>2</sub>. The indication of the strength of vitamin D in international units is based on experiments on rats ( $1 \text{ mg D}_2 = 1 \text{ mg D}_3 = 40\,000 \text{ I. U.}$ ).

In order to ascertain whether there was any difference in anti-rachitic effect between peroral and parenteral application in the therapy and prophylaxis of infants, numerous comparative investigations have been made. Generally speaking, similar results have been obtained by different authors in regard to treatment per os, apparently indicating a somewhat better effect with the use of D<sub>3</sub> (HARNAPP 1940, HEISLER 1940, HARTENSTEIN 1940, etc.).

As regards the parenteral supply of D<sub>2</sub> the statements are more conflicting. Several authors (NADRAI 1938, HEISLER 1940, TÜRK 1940, etc.) have observed a satisfactory effect, scarcely deviating from that of a corresponding dosage per os. On the other hand, NITSCHKE (1937, 1940), KLOTZ (1939) and BÖHM (1940) found — without being able to discover any satisfactory explanation —, that parenterally applied D<sub>2</sub> was almost without effect on their rachitis patients. BÖHM's and NITSCHKE's cases reacted quickly to D<sub>2</sub> per os.

Since 1938 we have tested anti-rachitic massive dose treatment, for prophylactic purposes, at Kronprinsessan Lovisa's Hospital for Children. Somewhat more than 200 premature infants (weight at birth under 2 500 gr) received a prophylactic massive dose when they had attained a weight of about 2 000 gr (or, if their weight at birth had exceeded that limit, about a fortnight after birth). The children included in the material, at the time when the massive dose was given, had not shown any signs of



rickets. The first cases received only 250 000 units, but it was soon found that this dosage was insufficient, and it was accordingly increased to 500 000—600 000 I. U., dissolved in 1—2 gr arachis oil.<sup>1</sup>

At first D<sub>2</sub> was given per os. As, however, vomitings sometimes occurred after such treatment, thus preventing the complete utilization of the vitamin, intramuscular injection was adopted, instead. In addition to D<sub>2</sub>, D<sub>3</sub> was used, and the great majority of cases were treated with the latter. 71 cases out of the whole material, who, apart from the massive dose had not received vitamin D were followed polyclinically with an observation period up to one year. Half of them were regularly examined with the x-ray as well as for calcium and phosphorus in the blood, determined with the method of E. Josephson (1940), whilst the remainder were examined for the most part clinically, with occasional Roentgen and determination of calcium and phosphorus. A small number received allaitement mixte, the others were breast-fed infants. Craniotabes, a slight rachitic rosary, or slight epiphyseal enlargements, as the only symptoms, were not regarded as undoubted signs of rickets, but were judged in conjunction with the x-ray findings and the calcium and phosphorus blood values. In 11 cases craniotabes was observed on different occasions during the first half-year, especially in infants under 2—4 months, without other signs of rickets (negative Roentgen; blood calcium and phosphorus normal). On this basis, it was found that, as shown by Table 7, seven infants, six of whom had received 500 000—600 000 units of vitamin D, had developed a slight rachitis in the course of the latter half of the first six months. In all these cases the rickets were revealed by the x-ray, whereas the clinical examination was negative in two of them (cases 2 and 3). In merely two cases out of the seven was the blood phosphorus value pathological. The phosphorus picture, however, it not considered entirely reliable in prematures, seeing that, despite the rachitis, normal phosphorus values are often found (HOTTINGER

<sup>1</sup> The preparations, Ultranol fortior etc., were kindly placed at the disposal of the clinic by A.B. Ferrosan, Malmö.

1928, HESS 1929, and others). It is of some interest to note that in two cases rickets developed during the warm half-year.

To recapitulate, the author, during a varying observation period of up to one year, followed 71 cases of prematures who had received a massive dose of 500 000—600 000 units of vitamin D for the prevention of rickets. In six infants a slight roentgenological rachitis was found during the latter half of the first six months. Viewed clinically, the morbid changes in these cases were but little marked. Some of the children, however, were not regularly controlled with Roentgen and chemical examination of the blood content. In these children no definite case of clinical rachitis could be observed.

*Table 1.*

Antirachitic prophylaxis for premature infants. (The figures in brackets indicate the cases which were followed mainly clinically.)

Observation period	3—4 m.	4—5 m.	5—6 m.	6—7 m.	7—9 m.	9—12 m.
Number of cases	71 (35)	65 (31)	61 (30)	57 (28)	52 (28)	45 (22)

The question whether vitamin D in large dose may cause damage has been studied by clinicians and pathologists since the first half of the nineteen-twenties, when MELLANBY observed tachycardia in children after a relatively large dosage of cod liver oil. AGDUHR (1925—1935) and a number of other investigators, in experimental studies of certain kinds of animals who had received cod liver oil, irradiated ergosterin etc. in large doses, found pathologico-anatomical changes in the heart blood vessels, kidney and other organs. Also in animals who had received pure vitamin D in large doses, he obtained, in certain cases, changes of the same type.

Changes attributable to large doses of irradiated ergosterin or cod liver oil have been reported, after clinical as well as pathologico-anatomical investigations, also in man (MALMBERG 1929, WILTON 1933, GERLACH 1936). BAMBERGER and SPANGER reported in 1928 that in the urine of 10 out of 11 children treated with

*Table 2.*  
Cases with demonstrable rachitis.

No.	Weight at birth, in g.	Dosage I. U.	Age	Roentgen (hand)	P.	Ca.	Clinical examination
1.	1.760	250 000 D <sub>2</sub> pr os	3 m. 13 d.	Especially within ulna, increased breadth of calcification zone, but sharp delimitation	2.8	12.3	Slight craniotabes, otherwise no signs of rachitis
2.	2.180	500 000 D <sub>2</sub> pr os	6 m. 28 d.	Slight enlargement of metaphyses. Slight irregular calcif. zone	5.3	14.3	No signs of rachitis
3.	2.060	600 000 D <sub>2</sub> i. m.	4 m. 12 d.	Bending out of metaphysis borders in ulna, slightly increased breadth of calcif. zones and some blurring in them	6.0	11.4	No signs of rachitis
4.	1.400	500 000 D <sub>3</sub> pr os	3 m. 22 d.	Calcif. zone somewhat increased in breadth, with sharp delimitation	3.5	12.6	Distinct craniotabes. Slight epiphyseal enlargements. No rosary
5.	1.400	500 000 D <sub>3</sub> pr os	3 m.	Diffuse decalcification at distal end of radius and calcif. zone nearly obliterated	5.1	14.8	Marked craniotabes, no rosary or epiphyseal enlargement
6.	1.890	500 000 D <sub>3</sub> pr os	4 m. 26 d.	Enlargement of metaphyses, slight increase in breadth of calcif. zones	7.4	11.8	Considerable craniotabes. No rosary or epiphyseal enlargement
7.	1.810	600 000 D <sub>3</sub> i. m.	6 m. 22 d.	Slight cup shape of distal end of ulna	4.6	10.6	Slight craniotabes. No rosary or epiphyseal enlargement

irradiated ergosterin they had observed red and white cells, cylindroids and albumin, which disappeared after the discontinuance of the medication. PUTSCHER in 1929, on dissection of a 5½-months-old child, who had received altogether 240 mg

irradiated ergosterin, observed macro- and microscopic calcareous deposits in the kidneys. He considered it highly probable that they were due to the vigantol.

After the introduction of the massive dose treatment, this question was brought up again. But pure vitamin D was then available and reports of changes which could be attributed to large dosages have been sparse, although the massive dose treatment had been applied on a large scale. In 10 infants who had received a massive dose, SCHALLOCK (1939), on dissection, could not show any organic changes, whereas BUFE in 3 out of 10 full-term infants with malfomations found renal changes with calcareous deposits in the tubuli and degeneration in the parenchyma. JOHNSON and WILTON (1944) have described changes of the D vitaminosis type in the kidney, heart and vascular system in four similar cases, the connection of which with vitamin D seemed very suspect.

These, however, were cases of non-viable children with grave malformations, whose tissue vitality at the time of the massive dose may be presumed to have been considerably reduced, with a lessened power of resistance to the large doses of vitamin D.

TÜRK has described 3 cases of transient albuminuria (two of which with cylindruria) after a massive dose of vitamin D per os. These children, however, were highly feverish (bronchopneumonia and otitis) which, as he himself considers probable, may have been the origin of the pathological urine finding.

From 39 patients in his material, the author has taken some 80 urine samples, usually at the end of the first week and at the end of the first month after the administration of the massive dose, without being able to discover in the urine any signs of renal damage.

AGDUHR and STENSTRÖM (1929—1930) were the first investigators who endeavoured with the electrocardiogram to verify the pathologico-anatomical investigations of the first-mentioned author and of other investigators regarding the noxious effect of anti-rachitic preparations on the animal heart. In thorough electrocardiographic studies on mice, rabbits and other animals who had received cod liver oil or vigantol, they showed prolonga-

tion of the P—R interval and the QRS time, a negative T spike etc. These distinct deviations, the connection of which with the medication seems beyond doubt, were, generally speaking, the same in all animals, irrespective of whether cod liver oil or vigantol has been used in the tests. The pathologico-anatomical findings corresponded to those previously described: different kinds of degeneration in the myocardium, calcareous deposits etc. They also observed a distinct regression in the electrocardiogram after the discontinuance of the anti-rachitic preparation. These results, however, could not be directly applied to man.

JUNDELL and STENSTRÖM (1931) followed with the electrocardiograph 21 infants ( $1\frac{1}{2}$ —4 months), who has received cod liver oil or vigantol continuously in fairly large dosages. They considered here too that they obtained the same deviations as in animals, though not so pronounced. Several objections, however, may be raised against the minute changes described. The prolongation of the P—R interval (in one-third of the cases 0.02 seconds) and the QRS time seems quite insignificant and may be explained by the growth of the infant. The changes in the conformation of the curve were almost exclusively localized in lead III and, with our present experience of the electrocardiogram, no certain pathological significance is attached to such a deviation. Moreover, several of the experimental children had infections which, as the authors themselves point out, might have given rise to the prolongation of the P—R interval. Similarly, transient infections, which had not been observed, may have been present. The vigantol used apparently contained other irradiation products besides pure vitamin D.

Similar objections may be made in regard to the small deviations which DOXIADES & UHSE (1933) and UHSE (1935) found in the S and T spikes in the electrocardiograms of children who had received vigantol or cod liver oil in a continuous dose. KIELHORN and RÜBENHAGEN (1938), in an extensive series of experiments on children, could not find any pathological changes in the electrocardiogram after protracted treatment with vitamin D.

Since the introduction of the massive dose treatment, the

question of electrocardiographic changes has acquired new interest. Nothing pathological in the electrocardiogram in connection with the massive dose could be observed (OPITZ 1937, SCHIRMER 1937 and others). HARNAPP (1937), in some cases, had given up to 22.5 mg vitamin D.

In some 40 cases the author had taken electrocardiograms before the massive dose and had controlled them with about 60 electrocardiograms taken after the lapse of some time, 15 of them within 2 months, the remainder at different times in the course of one year. Four of these cases may call for some discussion, the others show quite normal electrocardiograms.

RÄIHÄ (1936) and others often observed disturbances in the excitatory current and its conduction in the case of infants electrocardiographed during the first few weeks of life (occasionally even later) and an increase in the size of the spikes with advancing age. The changes were often of a very transient nature and appeared without other signs of heart affections and irrespective of acute infections. He regarded this variability as a manifestation of the poor development of the vascular system in the heart of these children. As for the increase in the size of the spikes, he considered it to be indicative of improved heart status. — This improvement was several times observed by the author in his electrocardiograph material after the administration of the massive dose.

Three children about 1, 4 and 7 months, respectively, on control after the dose showed deep  $Q_{III}$  spikes (Fig. 1 a and b). We know, however, as shown by ENGEL (1937), NADRAI (1941) and others, that deep Q spikes are an ordinary phenomenon in healthy infants. MANNHEIMER's (1940) normal material of older children, where in one-fifth of the cases  $Q_{III}$  was larger than one-fourth of  $R_{III}$ , points in the same direction. Thus a large Q spike cannot *per se* be regarded as pathological. In one child with a large  $Q_{II}$  and  $Q_{III}$  spike was found a slight elevation of the S—T segment, which, if it is the only change, is not a pathological sign (NADRAI 1941) (Fig. 2 a and b). But this change in conjunction with a deep Q spike suggests the possible occurrence of slight myocardial damage. Though acute infections among these children

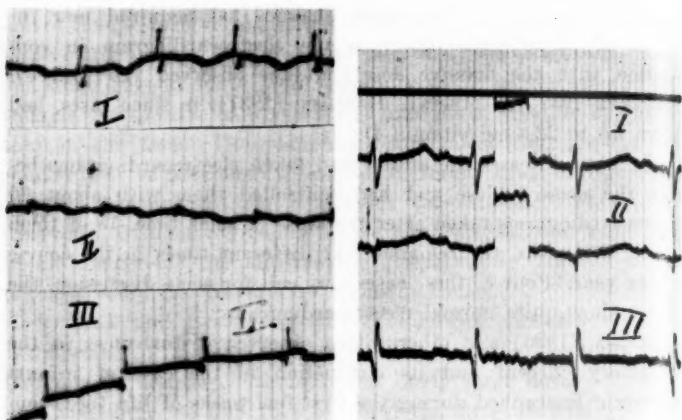


Fig. 1 a and b. 30.1.1940.

- a. Electrocardiogram taken on 16.2. 1940 before the massive dose treatment. Small initial complexes.
- b. The same patient as in a. Electrocardiogram taken about a month after massive dose treatment. Initial complex now more marked. Large  $Q_{III}$ .

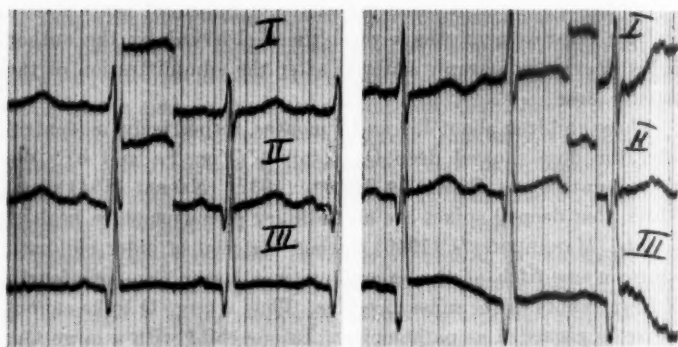


Fig. 2 a and b. 23.3.1943.

- a. Electrocardiogram taken one month after massive dose treatment. Normal electrocardiogram.
- b. The same patient as in a. Electrocardiogram taken 7 months after massive dose treatment. Some deep Q spikes and slight changes in the S-T segment.

are not known, transient infections are not uncommon and may leave traces in the electrocardiogram. In another case a very large R spike (32 mm) appeared in lead III. This, however, does not indicate myocardial damage, which should have given small excursions, but may be regarded as an index of the lability in the premature infant's heart. The slight above-mentioned deviations from the typical electrocardiogram, therefore, can scarcely be designated as indicative of a D hypervitaminosis. Just as after massive dose treatment of a premature infant an improvement may be shown in the electrocardiogram in the form of larger spikes, so may changes in the reverse direction be expected, as an index of the variability, without necessarily being regarded as of pathological significance.

### Conclusions.

It appears from the author's and earlier investigations that premature infants are relatively well protected against rickets after a massive dose of 500 000—600 000 international units of vitamin D. No clinical signs of damage to heart or kidneys could be found as the result of that treatment. But, just as in full-term infants with marked malformations, there is reason to expect a weaker resistance to large dosages of vitamin D, so we must ask ourselves whether the debility of premature infants does not *per se* entail a greater sensitivity to vitamin D. A prophylactic method, obviously, should not involve any risk of damage. However, the prophylactic massive dose treatment for premature infants has various advantages and should therefore be subjected to continued clinical testing. Even if, for the present, we may view this prophylaxis with some hesitation, we need not reckon with the risk of D-hypervitaminosis after therapeutic treatment with a massive dose for rachitic children showing a deficiency of vitamin D.

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## **Pernicious Anaemia in Children.**

By

**BENGT J. JONSSON.**

Several cases of anaemia in children are described as pernicious anaemia in medical literature. These cases, however, should be most critically assessed. The picture of the disease has not always been sufficiently clearly differentiated, and the investigations have frequently been incomplete. This is especially the case in reports of older date.

The child's, and especially the infant's haematopoietic apparatus is exceedingly labile. If great demands are made upon it, extramedullary blood formation and marked alterations in the circulating blood are apt to occur. Most cases of anaemia in children are cases of hypochromic anaemia, but even hyperchromic anaemia may, however, occur although rarely. In the latter case the causative agent is of minor importance. A hyperchromic blood picture may be present in conjunction with anaemia of entirely different genesis. The individual, and the constitution-conditional mode of reaction of the organism has a conclusive bearing on the origin of anaemia of this type. If, therefore, the blood picture in a child is hyperchromic and similar to that seen in pernicious anaemia, the diagnosis of true pernicious anaemia should not be established. It is of essential importance to discover the primary cause of anaemia, and special attention should be paid to the evolution of the disease.

In lymphatic leukaemia there may be presence of hyperchromic anaemia, nucleated red blood cells, a normal number of white blood cells and thrombopenia, a picture resembling in a high degree that seen in pernicious anaemia. Many of the cases referred

to as cases of pernicious anaemia in medical literature of older date were most likely suffering from lymphatic leukaemia.

FANCONI (1927) described a case of constitutional, hyperchromic, megalocytic anaemia in a child, and similar cases were reported by UEHLINGER (1929), van LEEUWEN (1933), WEIL (1938) and HJORT (1940). Anaemia of this type is associated with thrombopenia and haemorrhagic diathesis. Common to all these cases is the occurrence of malformations. The disease is fatal in spite of iron, liver extract and blood transfusion therapy. The bone marrow is, although hypoplastic, functioning. As may be seen, there is an essential difference between anaemia of this type and pernicious anaemia.

In the light of Castle's theory, a picture suggesting pernicious anaemia may be assumed to be due to the following reasons: 1) Defective production of »the intrinsic factor» in the mucous membrane of the stomach (true pernicious anaemia), 2) a diet lacking in »the extrinsic factor», 3) defective resorption of haematopoietic principle in the intestine, 4) disturbed function of the liver. There exist, however, certain megaloblastic anaemias, which fall outside the scope of this classification. WILKINSON and ISRAELS (1935) described a case of so-called »achrestic anaemia» which was refractory to liver extract therapy. The post mortem revealed that the liver contained haematopoietic principle. It might possibly be that the organism in these cases was incapable of mobilizing the haematopoietic principle, or that there was deficiency in some anti-anaemic, as yet obscure factor. DAVIS (1944) demonstrated that some of these cases of megaloblastic anaemia which were refractory to injections of fractional liver preparations, responded favourably to oral administration of proteolytic liver.

Anaemia resembling pernicious anaemia may be associated with celiac disease, due to disturbed resorption in the intestine. HOTZ (1924) described two cases of this type in patients aged four years and nine years and six months respectively. If the primary disease is cured, anaemia disappears spontaneously, without necessitating any specific anti-anaemic therapy. Pernicious anaemia resembling anaemia, and occasionally occurring in infants fed

with goat milk, most likely has the same pathogenesis. That this applies to animals, was demonstrated by ROMINGER and BOMSKOV (1935). The case of anaemia suggesting pernicious anaemia in an infant aged nine months, reported by FABER (1928) was doubtlessly a case of anaemia due to goat milk diet. RAGAZ (1939) described 13 cases of this type. All these were in perfect health at a later control examination. They manifested the typical constitution, viz. they were slenderly built and blue-eyed, had fair hair, manifested poor hair growth and pallor. COLE (1941) reported a case of anaemia in a child aged three weeks which might have been due to intestinal disturbances in conjunction with some infectious disease.

Anaemia suggesting pernicious anaemia has also been reported in conjunction with stricture of the small intestine. Symptomatic pernicious anaemia may also occur during pregnancy as well as with lues and helminthiasis. Anaemia of this type responds favourably to liver extract therapy, a fact which is of great importance.

Diagnosis of true pernicious anaemia is warranted provided: 1) that a hyperchromic macrocytic blood picture with megaloblastic haematopoiesis is present, 2) that other diseases which might suggest pernicious anaemia can be definitely excluded, 3) that only a treatment with liver and stomach preparations is effective, and 4) that the condition calls for the maintenance of this specific therapy. From this may be concluded that definite diagnosis should be established only after prolonged control of the evolution of the disease. The cases which were described previous to the introduction of liver extract therapy, can, therefore, only be vaguely assessed, and medical literature of older date will not be reviewed in the present paper.

ISELI (1934) published a case in which the presence of pernicious anaemia cannot be considered as definitely proved. KERSLEY (1935) described a case of »atypical megalocytic anaemia» in a boy aged eleven years. In spite of liver extract therapy having been successfully used, the diagnosis of pernicious anaemia cannot be considered as verified. Bachman (1936) reviewed from the literature 10 cases of hyperchromic anaemia in infants and re-

	Age	Haemo- globin %	Red blood cells	Colour index	Macro- cytosis
LANGMEAD, DONIACH, 1937	13 months	50	2 550 000	0.98	+
DEBRÉ et. al., 1939 . . .	6 years	40	1 480 000	1.4	+
MURPHY, 1939 . . . . .	11 years	39	1 980 000	0.99	+
POHL, 1939 . . . . .	13 years	47	1 700 000	1.4	+
ANDREASSEN, 1941 . . .	14 years	38	1 360 000	1.39	+
DEDICHEN, 1942 . . . .	9 months	41	2 120 000	0.97	+
NORDENSON, KARLSTRÖM, 1944 . . . . .	1½ year	20	1 100 000	0.91	+

ported a case of anaemia suggesting pernicious anaemia in an infant aged nine months under his own observation. In this case, however, anaemia occurred without any doubt secondarily, after some infectious disease and disturbances of nutrition. Even the cases which this author reported from the literature cannot be covered by the term pernicious anaemia. ADAMS and McQUARRIE (1938) described the case of a girl aged twelve years who in addition to anaemia presented endocrine disturbances. In this case too, there does not seem to have been definite evidence of the presence of pernicious anaemia. TEMPLETON (1939) published a case which was most likely due to alimentary causes. DAVIS (1944) reported a case of megaloblastic anaemia in a girl aged thirteen years. Myelographic examination revealed typical features, and the patient responded favourably to liver extract therapy. Nevertheless, this author believed that the anaemia was most likely due to some disturbance of nutrition.

The Table shows 7 cases in which diagnosis pernicious anaemia was definitely justified or at least possible. In some of these, however, the follow-up period was too short to permit of establishing definite diagnosis.

White blood cells	Myelogram	Achylia refractory to histamine	Helminthiasis	WR	Liver therapy	Follow-up period
8 500	?	yes	?	?	efficacious	3 months
3 500	typical	no	?	?	»	6 months
3 700	?	yes	?	?	»	3 years
4 600	?	yes	neg.	neg.	»	3 years
2 720	typical	no	neg.	neg.	»	2½ months
10 000	typical	{ achylia (EWALD)	?	neg.	»	2 years
4 900	typical	no	neg.	neg.	»	1 year

*Report of two Cases which came under the Author's own observation.*

At the Children's Hospital Norrtull, two patients in whom the diagnosis pernicious anaemia was established, were treated during the months September—October 1944. One of these, a girl aged fourteen years has been treated from 1934 onwards on four different occasions at this hospital, and her case was described in 1939 by MAGNUSSON and HAMNE (*Acta ped.* XXV: 189). The picture of the disease having considerably changed since then, however, a republication of this case may be considered justifiable.

*Case 1.* M-B. K. Girl, born June 30, 1930. Birth weight 3 770 g. Normal delivery. No history of blood diseases in the family. At the end of six weeks subsequent to the birth of the child, the mother developed paratyphoid fever (Breslau) and died on the eleventh day of her illness. The infant was recognized to be contaminated with the same infectious disease and was admitted to the Infectious Hospital of Stockholm where the patient was treated during ten months under the diagnosis of: paratyphoid fever (Breslau) + otitis media + secondary anaemia. During the first six months of her stay in hospital paratyphoid bacilli were observed in the faeces. The patient did not run any temperature nor did she suffer from diarrhea. She developed a purulent otitis from which she recovered at the end of two weeks. During the first six weeks of her life she was exclusively breast-fed, but when her

mother was taken ill she was put on a diet of diluted cow milk. When she was three months old fruit juice was added to the diet, and when she had attained the age of six months, she was given vegetable and fruit purée. Even Vigantol was administered. On her admission to the Infectious Hospital the blood findings revealed normal values. Several weeks previous to her discharge from hospital, however, she manifested the first symptoms of anaemia, viz. haemoglobin 53 per cent, red blood cells 3 480 000. She was given Ferrum reductum. This therapy was maintained after her discharge from hospital.

At the age of two years the child was put under the care of foster-parents who owned a farm. The foster-parents did not notice any signs of disease in the child, but when she was about three and a half years old, the district health officer noticed that the child did not seem to be in good health and referred her to a physician for examination.

On March 10, 1934, the patient was for the first time admitted to the Children's Hospital Norrtull (she was then aged three years and seven months). She manifested the typical symptoms of celiac disease. Weight 9 800 g. Height 87 cm. Stools were loose, voluminous and fatty. There was even presence of anaemia (haemoglobin 51 per cent). She was treated with iron preparations and put on a banana + apple diet which resulted in rapid amelioration of her general condition and in her recovery from anaemia. The blood picture was not thoroughly investigated. On June 4, the date of her discharge from hospital, haemoglobin was 89 per cent.

Subsequently, the patient was in good health until she had attained the age of eight years and seven months when she developed a bad appetite, loss in weight and manifested pallor. On January 1, 1939, she was admitted for the second time to the Children's Hospital Norrtull. On admission she was of surprisingly small height, extremely thin and manifested impaired tonus and a very pale, slightly yellowish tinged facial skin. Weight 19.5 kg. Height 115 cm. Stools were formed though rather voluminous and fatty. The essential of the picture of the disease was the pronounced anaemia. Haemoglobin 34 per cent. Red blood cells 1 330 000. Colour index: 1.33. White blood cells 4 200. There were nucleated red blood cells. The Price-Jones curve showed gross variation and a raised mean diameter. The red blood cells showed normal resistance to hypotonic saline solutions. Sternal puncture revealed: »Some features of the bone marrow picture are similar to those seen in pernicious anaemia (macrocytosis, normoblasts showing specific cell division-figures, hypersegmentation of segmented cells). On the other hand, the cell which is characteristic of pernicious anaemia, i. e. the megaloblast showing a typical nuclear structure, is absent. It is, therefore, a case of macrocytic anaemia and not of pernicious anaemia.» Gastric secretion was normal. Roentgen examination of the alimentary tract revealed apart



from a surprisingly long sigmoid flexure, no other alterations. Wasserman reaction was negative.

The patient was put on common mixed diet combined with iron therapy to which she responded most favorably. The blood picture, however, remained hyperchromic, and not even 4 injections of Compolon (2 ml on each occasion) produced a change in the picture. On March 4, she was discharged and presented a satisfactory general condition. Haemoglobin 90 per cent. Red blood cells 3 500 000. Colour index: 1.3.

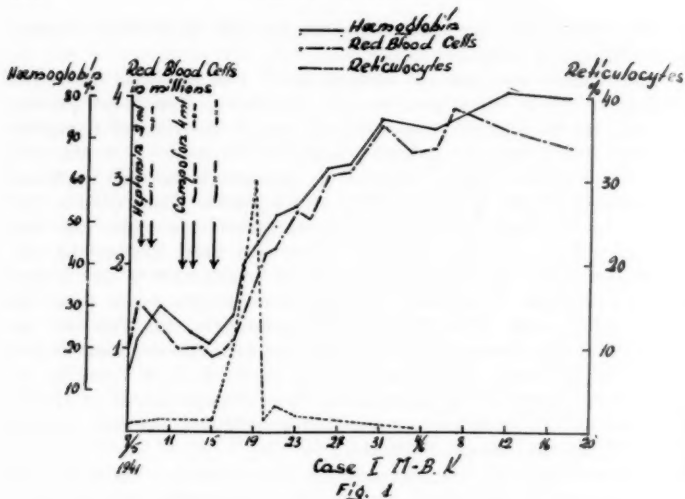
On her discharge the patient was instructed to continue the iron therapy, but she took the medicine occasionally only. During the subsequent two years she was in good health and manifested no steatorrhea. In the beginning of the year 1941 her appetite was again poor, she began losing weight and her complexion grew pale. In April she was reexamined and manifested then severe anaemia (haemoglobin 30 per cent). On April 22, she was admitted to the hospital of Ljungby. In spite of iron therapy and one liver injection (though only 2 ml Heptomin), the patient's condition impaired and on May 7, she was referred to the Children's Hospital Norrtull.

On admission her general condition was affected. The pulse was quick and soft. Respiration rapid. Her complexion was pale and grayish. She was extremely thin. Height 145 cm. Weight 22.1 kg. The general examination revealed a soft systolic murmur above the base of the heart. The liver was palpated at a level of two finger-breadths below the areus. Otherwise there was nothing abnormal.

Blood counts revealed: haemoglobin 15 per cent, red blood cells 1 000 000, white blood cells 9 500. Differential count yielded: Segmented cells 24 per cent, lymphocytes 73 per cent, mononuclears 3 per cent. Pronounced aniso-poikilocytosis and polychromasia, nucleated and basophilic red blood cells. The resistance of the blood cells was normal. Meulengracht 1 : 6. Sedimentation reaction 55 mm. Figure 1 shows the blood values during the later course of the disease. On May 7, sternal puncture revealed: »Preparation comparatively rich in cells. Slightly hyperplastic erythropoiesis. Typical megaloblasts. Myelopoiesis showing severe degenerative alterations. Absence of megakaryocytes. Slightly hyperplastic reticulum. Diagnosis: Marrow showing all the signs indicative of the presence of pernicious anaemia.» (Dr. Nordenson.) On May 16, there was, however, only to some extent remission of the symptoms.

Throughout the patient's stay in hospital, the stools were formed, of normal volume and not fatty. Vermis eggs were not demonstrated. The test meal revealed normal acidity values. During the first two weeks of the patient's stay in hospital she suffered from a respiratory infection and her temperature was slightly raised. Her appetite was poor and she felt tired. As soon as the blood values began to rise, however, her





general condition rapidly improved and she gained 3.5 kg in weight in the course of three weeks. She had been given normal diet. She was treated with liver injections and blood transfusion on two occasions; 200 ml were transfused on admission to the hospital and 90 ml on May 16. In addition, she was given iron throughout her stay at the hospital. On June 19, she was released from hospital looking healthy and was in excellent general condition.

Subsequently, she was followed up at the outpatient department and was treated with liver injections at intervals of 1 to 3 months. During the subsequent three years she was in good health, the blood values were, generally speaking, satisfactory though the blood picture remained hyperchromic. Steatorrhea was never manifested. She spent the summer of the year 1944 in a children's summer holiday camp. In May she had been given the last liver injection. During the summer she was supposed to follow a liver extract therapy per os (Binaemon 2 tabl., 3 times), but she neglected to take the medicine regularly and consumed only one third of the amount she had been prescribed. Towards the end of August, the patient's condition was again worse. On September 15, she was reexamined, and the blood count revealing haemoglobin 51 per cent, red blood cells 2 100 000 the patient was readmitted to the hospital.

At the examination she was of a striking pallor with a slight yellowish tinge. Her physical development was considerably below normal. Height 138 cm, weight 29.5 kg. (The patient was then aged fourteen years and

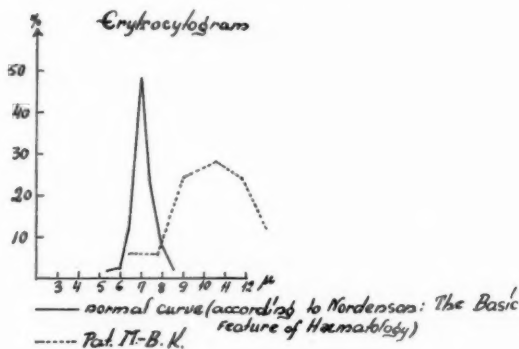


Fig. 2

three months.) As regards the superficial lymphatic glands there was nothing of note. The tongue had a normal aspect. The pharynx was normal. Heart and lungs normal. The abdomen had a normal configuration, liver and spleen were not palpable. There were no neurological disturbances. Blood count revealed: haemoglobin 54 per cent, red blood cells 2 500 000. Colour index: 1.04. White blood cells 4 000. Reticulocytes 1.2 per cent. Thrombocytes 334 000. The differential blood count yielded: segmented cells 46 per cent, eosinophils 2 per cent, lymphocytes 51 per cent, monocytes 1 per cent. No nucleated red blood cells. Moderate anisocytosis. Macrocytic blood picture (see Fig. 2). Bleeding time, 4 minutes. Coagulation time, 3 1/2 minutes. Determination of resistance: hemolysis began at 0.45 per cent, and was complete at 0.32 per cent. Sedimentation reaction 34 mm. Meulengracht 1 : 7. Sternal puncture revealed: »Preparation rich in cells. Myelopoiesis presenting marked disturbances of maturation. Hyperplastic and partly megaloblastic erythropoiesis. Scarcity of megakaryocytes. Reticulum to a high degree hyperplastic. The picture as a whole similar to that revealed in 1941. Diagnosis: Almost all features of the picture correspond to those seen in pernicious anaemia in adults. Orthochromatic megaloblasts though not quite as numerous as in adults.» (Dr. Nordensson.)

Apart from the presence of urobilin and urobilinogen the urine did not present anything of note. Stools were of normal aspect and volume. No vermiform eggs. The test meal revealed normal acidity values.

The patient who had not been given any iron, presented a serum iron value of 0.158 mg %. Treatment with injections of liver preparations (Hepatotal Novo) was instituted. After discharge of the patient from the hospital, the injections were continued at the outpatient department. Complete remission. The latest control examination (on December 21, 1944) showed: Haemoglobin 78 per cent, red blood cells 3 710 000.

*Discussion.*

MAGNUSSON and HAMNE published the reported case subsequent to the patient's stay in hospital which covered the period from January to March 1939. In 1934, the patient's appearance warranted the diagnosis of celiac disease, and in 1939, there still persisted some symptoms characteristic of this disease. In 1939, there was even presence of anaemia resembling pernicious anaemia, which, however, regressed satisfactorily subsequent to the administration of iron. This case was, therefore, considered to be a case of hyperchromic, macrocytic anaemia due to celiac disease. The authors believed that the cause of the disease most likely was paratyphoid fever from which the patient had suffered during the first year of her life.

Since then, the picture of the disease has considerably changed. In 1941, the patient manifested an extremely severe anaemia (Haemoglobin 15 per cent), but there were no signs indicative of a celiac disease. There is no doubt that the rapid and complete remission was exclusively due to the liver therapy. The small quantities of blood transfused to the patient cannot have played an important part in remission, nor can it be assumed that the iron therapy had a conclusive bearing on it, since during two weeks this medicine had had no effect whatsoever. The blood picture was in every respect typical of pernicious anaemia (hyperchromic, macrocytic anaemia, pronounced aniso-poikilocytosis and polychromasia, nucleated and basophilic red blood cells, comparative increase of lymphocytes). Even myelographic examination revealed a picture that in every respect resembled the one seen in pernicious anaemia of adults. As long as the liver therapy was maintained, the blood values remained at a satisfactory level, but as soon as the treatment was discontinued the condition of the patient impaired.

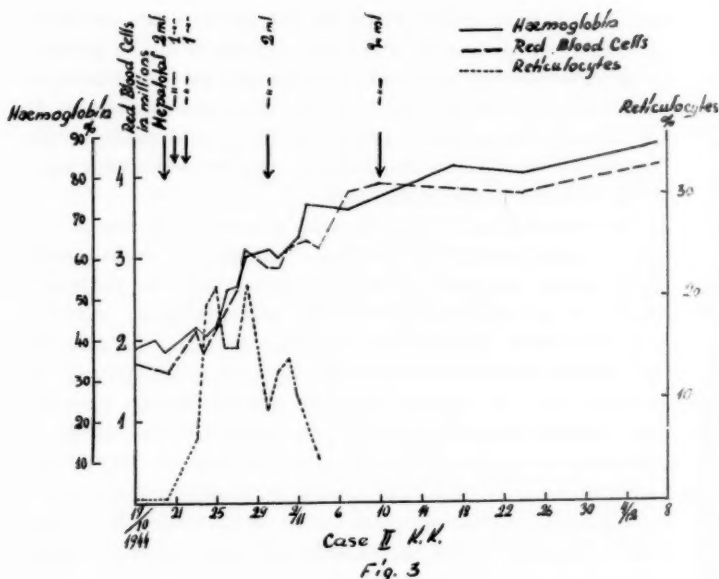
The blood picture and the evolution of the disease definitely support the diagnosis pernicious anaemia. One symptom, however, the presence of which is considered to be obligatory in pernicious anaemia, was missing, i. e. achylia of the kind that is refractory to histamine. On the other hand, cases of definite pernicious

anaemia have been described which did not manifest this symptom. ALSTED reviewed 34 cases of this type. Achylia is due to atrophy of the gastric mucous membrane and by this fact it is brought into relation to defective production of »the intrinsic factor». It might, however, be possible that an isolated disturbance of the last mentioned function occurs, without entailing any disturbance of the secretion of hydrochloric acid.

In the reported case the diagnosis of pernicious anaemia is justifiable, provided that the presence of other diseases the picture of which might suggest pernicious anaemia, can be definitely excluded. It is true that the patient had previously suffered from a true celiac disease, but in cases of this type anaemia usually disappears after the primary disease has been cured. In the present case, the patient had not manifested any symptom of this disease since 1941. On no occasion were signs of helminthiasis or lues demonstrable. In this instance differential diagnosis between an intestinal disease with defective resorption of haematopoietic principle is of major importance. The paratyphoid fever from which the patient had been suffering, might have been the cause of this disturbance. This, however, does hardly seem likely, since the patient at the time when this paper was written, did not manifest any signs of disturbed resorption and roentgenographic examination of the small intestine did not reveal anything of note.

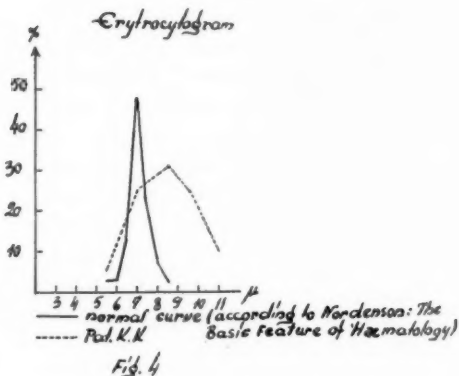
This patient was, therefore, in all probability suffering from true pernicious anaemia which had set in when she was ten years and six months old. Even two years earlier the patient had manifested a constitutional inclination to react with hyperchromic, macrocytic anaemia.

*Case 2.* K. K. Boy, born August 18, 1940. Birth weight 3500 g. Normal delivery. The only child. The grandfather on the father's side and the grandfather on the mother's side were cousins. There was no history of a blood disease in the family. The blood count findings in the parents were normal. During the first three months of his life the patient was breast-fed. At the age of five months, he was put on a diet of diluted cow milk and vegetable purée, and beginning from his eighth month, he was given a mixed diet. He had always been given an adequate diet. Vitamin D was administered during the winter months. The



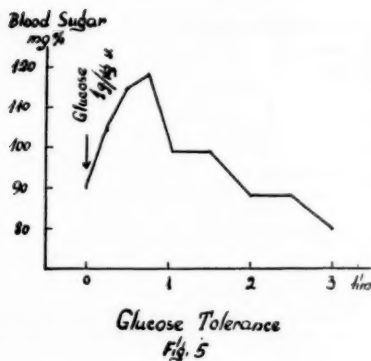
patient's physical as well as psychical development were completely normal. From the time he was three weeks old he was suffering from an eczema localized to the face, bend of the arm and knee. Otherwise he was in good health, and had a healthy complexion. From March 1942 (he was then aged one year and six months) on, within the course of a few weeks, his complexion became more and more pallid, and he felt tired and listless. Stools were loose but not very voluminous. His mother noticed blisters and small sores on his tongue. On April 16, the patient was admitted to the Children's Hospital of Linköping and presented on admission severe anaemia. The lowest blood values were: Haemoglobin 25 per cent, red blood cells 770 000. Marked megalocytosis. Thrombocytes were scantily present (55 000). Resistance of the blood cells was normal. Blood transfusion had an inconsiderable and merely temporary effect. He proved to be refractory to iron therapy. In the middle of May, subsequent to several injections of Heptomin, the anaemia ameliorated, and within the course of one month the blood values were normal as well as his general condition completely satisfactory.

Subsequently, he remained in good health and developed normally. He was meticulously followed up. Remissions lasted as long as 6 months and when, on rare occasions, the blood values had fallen more or less



considerably, he responded readily to liver injection therapy. No other anti-anaemic treatment was instituted. In December 1943 sternal puncture was performed, which revealed a picture that was in every respect typical of pernicious anaemia. On no occasion were signs of helminthiasis demonstrable. The last liver injection was given in June 1944. The patient was instructed to maintain the liver therapy per os (Hepaforte, 5 g daily, from September 7th on 2.5 g daily during fourteen days each month). In the long run, however, it proved impossible to induce the patient to consume the prescribed amount. In the middle of October he manifested again fatigue and pallor, and on October 17, 1944 at the examination at the outpatient department of the Children's Hospital Norrtull, the blood findings were: Haemoglobin 38 per cent, red blood cells 1 700 000. On account of these findings he was readmitted to the hospital.

At the examination he was found to be a bright, normally developed boy, aged 4 years. Height 96 cm, weight 15 kg. There was pronounced pallor with a slightly yellowish tinge. No cutaneous bleedings. An insignificant dry excema was present on the back of his hands and in the bend of his arm. His tongue was of bright red colour and smooth though not presenting any ulcerations. Superficial lymphatic glands normal. Examination of the heart revealed: a fairly sharp systolic murmur on the sternum. Blood pressure: 95/40. The Lungs were normal. Abdomen: liver and spleen not palpable. Neurological examination did not reveal anything of note. The blood count findings were: (Fig. 3 shows the values of haemoglobin, red blood cells and reticulocytes.) White blood cells 5 000. Thrombocytes 88 000. The differential count findings revealed: segmented cells 14 per cent, staff cells 2 per cent, eosinophils 5 per cent, lymphocytes 79 per cent. Solitary nucleated red blood cells.



Pronounced aniso-poikilocytosis and polychromasia. Megalocytosis (see Fig. 4). Hypersegmented leukocytes. Bleeding time 4 minutes. Coagulation time 8 minutes. Determination of the resistance yielded: hemolysis begins at 0.42 per cent and is complete at 0.34 per cent. Sedimentation reaction 29 mm. Meulengracht 1/8. Serum iron 0.229 mg per cent. Wasserman reaction negative. Mantoux test up to 1 mg negative. Urine: urobilin +, urobilinogen +, Hammarsten —, Heller —, Almén —. Sediment: nothing of note. Faeces: normal quantities and containing fatty acid crystals in moderate quantities. No vermis eggs. Glucose tolerance test yielded a normal blood sugar curve (Fig. 5). Sternal puncture was performed on October 19. The findings were: »Preparation rich in cells. Myelopoiesis presents severe disturbance of maturation and toxic alterations. Megaloblastic erythropoiesis. Severe disturbance of maturation. Normal percentage of megakaryocytes. Reticulum to a high degree hyperplastic. Diagnosis: »typical megaloblastic marrow. In every respect similar to that of pernicious anaemia in adults. In this instance the picture is, however, to a high degree toxic» (Dr. Nordenson). Fractionated histamine test meal revealed *normal* gastric secretion. Roentgenological examination of the esophagus, stomach and intestine did not reveal anything abnormal. Electrocardiographic examination showed that the myocardium was slightly damaged.

The patient was solely treated with injections of liver preparations. In conjunction with remission there was an increase of thrombocytes (300 000) as well as a decrease of serum iron (0.115 mg per cent) and of lymphocytes (30 per cent). Simultaneously, the general condition rapidly ameliorated, and on November 4, 1944, on his discharge from hospital, he had a florid complexion and was in excellent health. He remained healthy and at the latest examination on January 1, 1945, haemoglobin was 81 per cent and the red blood cells 4 000 000.

*Discussion.*

The blood alterations presented all the characteristics of pernicious anaemia, viz. hyperchromic, macrocytic anaemia with relative increase of lymphocytes, hypersegmented leucocytes, thrombopenia, increase of serum iron, moderate increase of blood-bilirubin. Even the other symptoms were characteristic. The patient manifested glossitis though gastric secretion of hydrochloric acid was even in this case normal. The urine contained urobilinogen.

Reaction to liver therapy was in every respect typical, and all blood alterations regressed subsequent to remission. The evolution of the disease furnished definite evidence of the necessity of maintaining the administration of liver extract preparations.

The presence of helminthiasis, celiac disease and lues could be definitely excluded. The diet was throughout fully adequate, and there were never any signs of defective resorption in the small intestine. In this case the disease must be definitely considered as pernicious anaemia which had set in when the patient was one year and six months old.

**Summary.**

Diagnosis of pernicious anaemia is justifiable provided that 1) there is presence of a hyperchromic, macrocytic blood picture with megaloblastic haematopoiesis, 2) that all the diseases the symptoms of which might suggest pernicious anaemia are definitely excluded, 3) that liver therapy alone proves to have a definite effect, 4) that the condition calls for maintenance of this specific therapy.

On the basis of these criteria the cases of pernicious anaemia in children reported in the literature up to date, are assessed. In seven of these the diagnosis of pernicious anaemia is considered to be either fully justifiable or at least possible. Description of two new cases in which the mentioned prerequisites were definitely demonstrated. The disease set in, in one patient at the age of one year and six months, and in the other at the age of ten years and six months.



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FROM THE PEDIATRIC CLINIC OF KAROLINSKA INSTITUTET AT KRON-  
PRINSESSAN LOVISA'S CHILDREN'S HOSPITAL, STOCKHOLM.  
HEAD: PROFESSOR A. LICHTENSTEIN.

## **Bacteriological Examination of Throat Tests from Children.**

By

**KURT KAIJSER.**

The following short synopsis gives the results of a bacteriological examination of throat tests taken from 385 children aged from 1 month to 13 years, who have been treated at Crown Princess Louise's Children's Hospital for lobar pneumonia, broncho pneumonia, bronchitis or pharyngitis.

The object of the investigation is to give a short orientation of the throat flora in children suffering from infections of the respiratory tract.

The bacteriological analysis has been carried out chiefly in the bacteriological laboratories of the Department of Public Health (Hälsövärdnsnämndens Bakteriologiska Laboratorium) in Stockholm.

The method of making the tests has been as follows: the throat test has been taken as soon as possible after the child has been admitted to hospital. It is well known that children experience a certain difficulty in expectorating and therefore the tests, in accordance with generally accepted principles, have been made by swabbing the posterior wall of the pharynx and, more especially, the region of the *epipharynx*, with a small swab. This is easily done if the swab is attached to a bent probe. More often than not the child will cough when the test is being taken and the swab thereby further enriched with material for the bacteriological culture. The swab is then placed in a test-tube containing grape-sugar bouillon which is immediately placed in the thermostat.

About twentyfour hours later the culture has become a subject for closer bacteriological analysis.

The examination includes a relatively small number of cases and consequently does not permit the drawing of any very exact general conclusions. Nevertheless the material should be representative of a clientele of children in a Swedish City and has its interest for making a comparison, for instance, with the foreign investigations given below.

On reviewing the results, the material has been classified in regard to the occurrence of certain main groups of bacteria such as streptococci, staphylococci, pneumococci and so on.

Before the introduction of modern chemotherapy, the possibilities of an active therapy in pneumonia was often dependent upon the possibility of determining the bacteriological diagnosis of that disease. This gave rise, amongst other things, to the intensified and improved bacteriological diagnosis of the different species of pneumococci. But even though the importance of type diagnosis has been somewhat lessened by the introduction of modern chemotherapy, there is no reason why bacteriological diagnosis should be wholly neglected.

In this synopsis my interest has been especially directed towards the appearance of the different pneumococci species in this children's material. No attempt has been made to compare the prognosis of infections of the air passage caused by different infection media. I consider that the material is far too small to allow any definite conclusions to be drawn especially when one takes into consideration the fact that the examinations include a period when a number of different methods of treatment came into use.

It should be further pointed out that one has no right to infer that the infection was caused by a specific bacteria just because that particular bacteria has been found in the throat test. In order to authenticate such a conclusion it would be necessary to prove the existence in the blood of the patient of certain specific agglutinins for the said bacteria and preferably in increasing strength during the course of the disease. Similar examinations have been made by, amongst others, CLAUSEN, FRIDERICHSEN and

LÖFSTRÖM and they show that a part of the pneumococci which can be found during the course of the above infections of the air passage, quite possibly are not the cause of the disease but are merely saprophytes.

It would seem, for instance, that it is not altogether impossible that pneumococci species such as VI and XIX appear to be less virulent in adults whilst they are considerably pathogenic for children.

In my material I have, as will be seen from Table I, classified the cases partly in accordance with the nature of the disease and partly in accordance with the kind of bacteria. Under the heading »Mixed Bacteria Flora» are cases with bacteria coli, Pfeiffer or suchlike as well as such there one could show three or more bacteria groups in cultivation.

Streptococci, which are species often classified as  $\alpha$ ,  $\beta$  and  $\gamma$ , have been placed in this synopsis under a common group. The same thing applies to the staphylococci group.

Table 1.

Bacteriological diagnosis of 385 throat tests in different diseases.

	Lobar Pneumonia	Broncho Pneumonia	Bronchitis	Pharyngitis	Number
Pneumococci (Defined species)	26	93	15	16	150
Pneumococci (Un- defined species)	8	52	10	2	72
Streptococci . . .	4	32	8	0	44
Staphylococci . .	1	10	4	0	15
Staphylo- and Streptococci . .	14	34	8	4	60
Mixed Bacteria Flora . . . . .	7	27	5	5	44
	60	248	50	27	385

It will be seen from Tab. 1 above that a large number of cases of acute infections of the air passage were caused by other bacteria

than pneumococci. That a relatively large number of cases have come within the group of pneumococci undefined species, depends on the fact that I placed there partly such pneumococci which, by ordinary methods, could not be grouped and partly such where (until a few years ago) test serum was not available.

In order to make a special study of the appearance in different diseases of pneumococci of the defined species, the cases have been classified in accordance with the following Tab. 2. (In 5 cases two different species were found, on cultivation, in the same patient.)

Table 2.

Classification of pneumococci species in different diseases.

Species	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV	XV
Number . . . .	14	2	6	6	3	10	23	3	14	2	1	1		14	2
Deaths . . . .	2		3				1							1	
Lobar Pneumonia . .	6		1	1		2	6		1					1	
Broncho- pneumonia . .	7	2	5	5	3	6	11	3	11	2	1	1		8	2
Bronchitis . .							2							3	
Pharyngitis . .	1					2	4		2					2	

Species	XVI	XVII	XVIII	XIX	XX	XXI	XXII	XXIII	XXIV	XXV	XXVI	XXVII	XXVIII	Total
Number . . . .	3	2	5	15	3	5	5	6	2	1	3	3	1	155
Deaths . . . .				1				1						9
Lobar Pneumonia . .	1			4			1	2						26
Broncho- pneumonia . .	2	2	5	9	3	2	2	3	1	1	1	2		100
Bronchitis . .				1		2	2		1	0	0	0		11
Pharyngitis . .				1		1		1			2	1	1	18

Table 3.

Examination of the occurrence of pneumococci species.

Author	Country	No. of cases	Age	Species frequency (Sinking from the left)
BULLOWA	U. S. A.	3 720	Adult	I, III, II, V, VII, VIII
BERGLUND, LÖF- STRÖM & STRAN- DELL	Sweden	351	Adult	III, I, VII, VIII, IV, V, XVIII, XIX, VI
ÅSKLUND, SJÖ- STEDT & VAHLNE	Sweden	275	Adult	I, III, V, VII, VIII, X, XIX
NEMIR	U. S. A.		Children	VI, XIX
PFAUNDLER & SCHLOSSMANN	(various countries)	1 668	Children	I, XIV, VI, XIX, V, III, IV, VII, II
			0—2 years	XIV, VI, I, XIX, IV, VII
			2—12 »	I, XIV, V, VI, VII, III, IV
VAMMEN	Denmark	304	Children	I, VI, XIX, VII, III, XIV
			0—3 years	VI, XIX, I
			3—12 »	I, VII, VI, XIX
FRIDERICHSEN	Denmark	108	Children	VI, I, VII, III, XXIII, XIX, XV, IX
			0—2 years	VI, XXIII, XIX, III
			2—8 »	I, VII, VI, III
CLAUSEN & FABER	Denmark	20	Children	VII, I, III, XIV
BJØRNSSON	Norway	54	Children 7—14 years	III, VIII, IV, I, VI, XVII, XV, XVI, XIX
RÖMCKE & VOGT	Norway	144	Children 0—10 years	I, III, VII, VIII, IV, XIX, XVII
KAJSER . . . .	Sweden	155	Children	VII, XIX, I, XIV, IX, VI, III, IV, XXIII,
		73 {	0—2 years	XIV, XIX, XVIII
			2—14 »	VII, VI, IV

It will be seen from Tab. 2 above that the occurrence of pneumococci in groups of a higher number are less than those within a lower number. This coincides with similar observations by other authors.

In my material, species VII, XIX, I, XIV and IX are most usual. They are given here after a sinking frequency beginning with species VII which was the most frequently occurring. 52 % of all pneumococci of the defined species are found amongst those mentioned species.

With regard to fatal cases the figures are too small to enable one to give any definite opinion. In the meantime more than half come under species III and I, which are even stated by other authors as being especially malignant for children.

In 73 cases, which are classified in accordance with the different ages, it appears that in ages from 0 to 2 years the most usual species were XIV, XIX and XVIII.

As a basis for the appearance of the different pneumococci species in my material, a certain amount of information from other authors is given in Tab. 3. Here I have referred partly to same examinations on adults and partly I have desired to compare the conditions in Children in other countries especially those bordering Sweden.

In comparing the conditions between adults and children, one finds that, in the latter, species XIV and XIX are considerably more frequent but that otherwise a certain similarity exists in the distribution of species.

If one compares the information about the presence of pneumococci species in children in accordance with the above investigations one will see that there is much agreement between the species frequency in different countries.

### Summary.

An investigation of the bacteriological diagnosis of throat tests made on 385 children aged from 1 month to 13 years who have been treated at the Crown Princess Louise's Children's Hospital (Kronprinsessan Lovisas Barnsjukhus) in Stockholm for acute infections of the upper air passage.

In 155 cases of pneumococci of the defined species one could show that species VII, XIX, I, XIV and IX, in the order given, were most common. These five species comprised 52 % of all species.

In children under 2 years of age, species XIV, XIX and XVIII were, in the order given, the most usual.

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### **Three years' Prophylaxis against Rickets in Prematures, with D<sub>2</sub> Massive Dose.**

By

**G. KLACKENBERG.**

In the treatment of manifest D hypovitaminosis, the clearly indicated procedure is the administration of vitamin D in a massive dose. The successful results of that treatment have naturally led to attempts to transfer the method to the far more important field of prophylaxis. The prophylactic effect — lasting for three or four months — of vitamin D in a massive dose in the case of full-term infants has been attested from many quarters.

Drawing the logical conclusion from these findings, GRASER proposed that all full-term infants should receive from midwives or maternity nurses a sufficiently large single dose of vitamin D. Even if we may question the utility of treatment on these lines for full-term infants, it should, under given conditions, be of the greatest value for prematures. Their liability to rickets is considered by ABT, the well-known American pediatricist, to be such that, as he neatly phrases it, »in spite of everything you do with prematures they are likely to develop rickets».

That prematures during the course of their first half-year are particularly liable to the development of that disease is due to the relative rapidity of their growth, their enforced indoor life, and perhaps also to a calcium deficiency at birth.

Rickets as a rule does not set in with manifest symptoms until after the lapse of two or three months, and it was formerly the practice to defer the administration of vitamin D till that time.

In the course of the last few years, however, it has been insisted — particularly in America, but also in Sweden —, that

rachitic prophylaxis for prematures has its maximum value when it is started at a very early date, preferably during the first week of life. Thus, MALMBERG, by a continuous daily supply of 10 000 units of vitamin D<sub>3</sub>, interrupted merely by brief spells without medication, succeeded in keeping prematures (weighing up to 2 000 grams at birth) free from any signs of rickets, even when viewed roentgenologically.

The chief drawbacks of this continuous treatment are that its efficacy is dependent on the care with which it is applied by the mother, and that the vitamin supply has to be restricted when a tendency to diarrhea is observed. When vitamin D is administered in a single dose, such drawbacks will, of course, be eliminated, and the small saving involved is an additional item on the credit side.

Thus, so far as concerns the actual administration of the vitamin, the advantages of a massive dose prophylaxis for prematures are obvious. The questions with which we are confronted are 1) whether such a dose is sufficient, and 2) whether there are any counter-indications.

Investigations giving a reply to the first of these questions are by no means numerous. WINDORFER, in a series of 50 carefully observed cases of prematures, arranged them in two divisions, one of which was treated with the massive dose, the other either with the ordinary more or less continuous prophylaxis or with ultraviolet radiation. The single dose amounted to 10 mgr D<sub>3</sub> (400 000 international units) and was administered at the age of six weeks. The continuous treatment consisted of 6 drops of Vigantol daily (about 2 500 units of D<sub>3</sub>), commencing at the said age. Ultraviolet radiation for the group in question was given every other day. Afterwards all the children were examined every 4th—8th week during an observation period ranging from 3 to 16 months.

Summing up the results of this test, WINDORFER considered it evident that the massive dose prophylaxis was satisfactory in the majority of cases, whereas the continuous and ultraviolet treatments were more often disappointing. The designation »satisfactory» refers to the clinical observations. With the x-ray, slight

indications of rickets were observed in almost all the children, even those treated with a massive dose.

In 1940 STRÖM followed 16 prematures during four months after a massive dose of 100 000 units per kg of body weight without being able to diagnose rickets in any of the cases.

ZELSON in 1940 reported an investigation on 46 prematures, in which the children had received a massive dose varying between 300 000 and 600 000 units, and different vitamin D preparations orally or parenterally. Vitamin D was supplied at the age of 2—4 weeks. In his summary, the author states that the children had been controlled up to an age of between 44 and 279 days, and that during this period no rachitis had been observed in those who had received 600 000 units of D<sub>2</sub> or D<sub>3</sub> parenterally. If we examine his figures closely, however, it will be seen that only one of the children who had received D<sub>2</sub> parenterally was controlled for as long as about 9 months, whereas the examination of the others was terminated after at most 62 days, in the majority of cases merely 30.

In a comparison between 23 cases treated with a massive dose and 15 controls without any supply of vitamin D whatever, TÜRK (1940) found that the result of the massive dose protection was extremely satisfactory. He gave 5—10 mgr D<sub>2</sub>, that is 200 000—400 000 international units, at an age of 3 weeks at earliest, the average age being 2 months. Unfortunately, no data are given in regard to the weight at birth, the principle on which the controls were selected, the time of x-ray examination, etc. That better results were obtained with the prematures treated with a massive dose is not at all surprising. What does seem astonishing is his statement that all the 23 children, with the exception of a twin, were free »von röntgenologisch fassbaren Rachitiszeichen«. Besides craniotabes, which may have had another genesis, and which nearly all of them showed sooner or later, a »rachitic rosary» and a slight indication of Harrison's groove were observed in four of the children.

Thus the question as to how far it is possible to prevent rickets in prematures by the administration of a massive dose has not been cleared up. Either the dosages tested had not been suitably

adjusted with a view to full protection, or else the time for the administration of the dose had not been wisely chosen. In view of MALMBERG's previously mentioned investigation, we must ask ourselves whether the excellent results of this continuous drop treatment, in addition to the amount of the dose (in the course of 3 months it would be equivalent to the supply of at least 600 000 units of vitamin D) are not partly due to its having been started as early as at the end of the first week of life. In non-treated cases, rickets in prematures is not only severer than in full-term infants, but also manifests itself earlier. Some cases where serological and roentgenological indications of rickets could already be observed in prematures at the age of two or three weeks have recently been described by VON SYDOW. In one case the signs were already noticeable at the age of 12 days.

In views of these considerations, it is evident that prophylaxis should commence at the earliest possible date, preferably during the first week of life. This applies also to the massive dose treatment. The probability that the utilization of the vitamin supplied will be hindered by defective resorption conditions in the premature infant's intestine is naturally greater, the younger the infant. However, feces analyses made by WINDORFER for a few days immediately following the administration of the massive dose indicate that the loss is quite insignificant. More than 95 % of the vitamin had been resorbed and thus had evidently been utilized by the system. Six such cases were examined.

At Norrtull Hospital the rachitic prophylaxis for the prematures confined there has for several years taken the form of massive doses (Ultranol fort. 500 000 units  $D_2$ ). Since 1943 it has been given in the course of the first few days after admission. This does not imply that the administration of the dose was always made during the child's first days of life, as, owing to lack of accommodation or other reasons, the children are sometimes kept at a maternity hospital for a number of days before they can be received at Norrtull Hospital.

The investigation reported here was in the nature of an after-control of the prematures who had been treated with the massive dose for prophylactic purposes. The primary object of this control

was to ascertain how far they had escaped rickets and thus to form some idea regarding the practical value of the prophylaxis. With this technique, there was no question of an analysis showing the occurrence of subtle signs of rachitis. All that was desired was to obtain some basis for judging the probability of marked rachitic changes in these children during the course of the next few years.

In addition to the routine examination for the typical rachitic symptoms (rachitic rosary and girdle, epiphyseal enlargements, retardation of dentition and of fontanel closure, etc.), the wrists were also x-rayed.

According to WIMBERGER, skeletal changes as the sequelae of rachitis are visible on the roentgen plates. They take the form of streaks of dense calcareous deposits, of epiphyseal deformations, or of a marked contrast between the fine-meshed metaphysis and the coarser spongiosa in the remainder of the shaft. When a lengthy space of time has elapsed between the onset of the disease and the subsequent examination, the value of these diagnostic signs is considerably reduced by transpositions and levelling-down of the structure. For this reason, sweeping conclusions could not be drawn from the negative roentgen pictures of children who had received a massive dose at a very early date. On the other hand, it seemed very desirable that all the children, even the older ones, should be included. The clinical signs, however, remains longer.

#### *The author's material.*

The prematures thus subjected to a control examination, after discharge from the hospital (*v. infra*), were 100 in number. Though, because of some mortality among the little patients, this material does not include all those nursed at the hospital since the inception of the massive dose treatment, it does not represent any special selection. All those who at the termination of the examination would be at the least about three months old were sent for by letter or telephone to the parents or guardians. The great majority of those with whom we thus got into touch willingly complied with our request. Merely a few failed to respond, and a somewhat

larger number could scarcely be reached, having moved from Stockholm.

The children came from families socially representing a cross section through the community. Among them we see the only child from the »upper ten» of the villa suburb with private nurse and family doctor, side by side with the illegitimates from the slum districts. In a rough grouping into social classes somewhat more than half could be ranged among families of small means, four or five were upper class, whilst the remainder represented the large group of employees in the public service or comparable income-classes.

Out of these hundred premature, 28 (including a triplet trio) had been born in plural birth. Though some of the twin pairs had been dissevered by the death of one of them during parturition, the survivor was naturally included in the twin group.

The weight at birth varied from 1 250 to 2 500 grams. Three of the infants were somewhat heavier at birth, but on admission to the hospital had fallen below the 2 500 gram limit, and were classed under *debilitas congenita*.

The number of children in the several weight-classes was as follows:

1 000—1 500 gr . . . . .	7
1 500—2 000 " . . . . .	34
2 000—2 500 " . . . . .	59

In somewhat more than half the cases the massive dose had been given — regardless of the child's weight at birth —, during the first week of life. The number of children who received the vitamin dose during the first few weeks of life or somewhat later is given in tabular form below. The table also shows that the regular administration of the dose at such an early stage was not started to the year 1943.

Days after birth	Number of children	Before 1943
1— 7	57	0
8—14	27	11
15—30	11	6
30	7	4

The entire amount of cod liver oil was not supplied all at once: the 500 000 units of D<sub>2</sub> were divided, as evenly as possible, into two portions, one of which was given at the time shown in the above table, the other, with tolerable regularity, one week later. As each child had its separate tube, it did not matter much if the division into the two portions was not perfectly exact: the total amount was, of course, in any case the same. The infants who could swallow were spoon-fed with the oil — previously warmed to render it more fluid —, in connection with a meal. In order to ensure the thorough utilization of the oil in the spoon and little tube, it was washed down with milk. The children whose swallowing reflex was not in proper action, were supplied with the oil through a feeding tube. In such cases it was washed down still more thoroughly, as otherwise a considerable amount relatively to that supplied (merely 1 cc at a time) might have been left in the feeding tube. If a child vomited within an hour or so afterwards, the same dose was given again. — In one case, for some now unknown reason, a child received merely 250 000 units.

During the three months immediately following the administration of the massive dose (setting aside two cases where 10 drops of concentrated cod liver oil were supplied daily for one and two months afterwards), the infants received no further supply of vitamin D whatsoever. As a rule the infants were not kept at the hospital after the time when they could maintain a normal temperature and effectually suck the breast. By that time they had as a rule attained a weight of 2 500—3 000 grams. They were then returned to their own homes or, in certain cases, to homes for mothers or children. They were sent with letters of recommendation to the proper Child Welfare Centre, which in most cases undertook the further supervision of the child. The nurse employed there was informed in writing that the child had received a massive dose. This doubtless explains why, as above mentioned, merely two of the infants had received an additional supply of vitamin D within three months after the massive dose treatment.

Endeavours were also made, by questioning the mothers, or



by examining the records of the Child Welfare Centre or the doctor's prescriptions, to form some idea as to the amount of vitamin D which the children had received after the lapse of the three months. In this respect there were great variations. Three infants had not received a drop of cod liver oil nor any ultraviolet raying at all. These infants, it should be noted, had not been registered at the Child Welfare Centre. On the other hand, it transpired that some of the infants had received several massive doses, in one case probably three in addition to that given at the hospital, and in three cases two new doses of Ultranol fort. within six months after the first. In addition, a general survey showed a miscellaneous collection of trade preparations of vitamin D, with a variety of different dosages. Latterly Guttae AD vitamin, in a dosage of 10 to 20 drops per day, seems to have predominated.

The control period varied from 3 months to 34, averaging 12—18 months after the administration of the massive dose.

#### *Results.*

All the children in whom clinical or roentgenological signs or sequels of rickets were observed showed merely slight traces of that disease. No deformations or marked rachitic residues could be found. Such lesions as could be determined by palpation (rachitic rosary or girdle, or epiphyseal enlargements) were designated in almost all cases as rather insignificant. Here, of course, we must reckon with the possibility that some of the judgments may have been subjective. This, however, is one of those risks that can scarcely be avoided in an investigation of this nature. In order, so far as possible, to eliminate that source of error, the palpatory diagnosis made by one of the hospital doctors was occasionally checked by comparison with a completely unbiased judgment on the part of one of his colleagues. As a rule, the correspondence between the two independent medical opinions was very good.

Practically all the Roentgen plates taken during this investigation were examined by the hospital roentgenologist.<sup>1</sup> He gave an

<sup>1</sup> I take this opportunity to convey to Dr OLIVER AXÉN my cordial thanks for his very valuable assistance in the examination of the Roentgen plates.



opinion in writing and demonstrated the photographs to the assembled medical staff of the hospital during the Roentgen round.

It is noteworthy that, as shown by the following figures, the clinical judgment indicated the presence of rachitic residues in a considerably larger number of cases than the roentgenological finding:

Roentgen pos. . . . .	9 cases
Clinically pos. . . . .	19 "

Cases where, for example, merely a slight enlargement of the malleoli was observed were not regarded as clinically positive. Isolated, insignificant changes of this nature need not necessarily be supposed to have any connection with rickets. The rule was that such slight changes should not be designated as positive unless they were found in conjunction with other skeletal lesions. With one exception, the Roentgen-positive cases were found to be also clinically positive. The single exception was a twin whose weight at birth was merely 2 100 grams, and whose brother likewise showed rachitic residues on clinical examination. The Roentgen picture revealed a cupping of the ulnar epiphysis, with markedly calcified, sharp borders. No enlargement of the malleoli could be shown on palpation, nor any rachitic rosary or girdle, but the forehead was somewhat too large and prominent. At the age of nine months the fontanel in this premature measured  $2 \times 2$  cm. The changes thus observed should perhaps be regarded as indicative of rickets.

The relatively small numbers of Roentgen-positive cases may perhaps be viewed merely as an indication of the structural changes through which the growing bone was passing. The lesions found on palpation were of a more permanent nature.

In order to estimate the factors involved in the poor clinical results in these 18 cases, they were examined from different points of view. Endeavours were made to ascertain whether these cases differed from the others with respect to weight at birth, plural birth, season of birth, the stage at which the massive dose was given, a later treatment of D-vitamin, infections or social conditions.

As regards the first of these questions, it can be stated that the low *weight at birth* had no bearing on the problem. The overwhelming majority of the rachitis-positive cases, both absolutely and relatively, were found in the group 2 000—2 500 gr. weight at birth.

About one-third of the entire material consisted of plural-birth children, mostly twins. Seeing that such children represented more than half of the rachitis-positive cases, it appears that liability to rickets is distinctly greater in *plural-birth* children. This accords with the results obtained by WINDORFER in his previously mentioned investigation.

The *season of birth* was found to be a factor of no significance in this enquiry. The number of rachitic children born, respectively, during the light and dark seasons of the year was approximately in the same proportion. This may seem a somewhat surprising result, but it will be found less curious if we consider how very cautious the mothers are in exposing their premature children to the ultraviolet rays of the sun. As a rule the infants lie well covered and muffled up when the windows are opened a while for ventilation.

Only four of the nineteen had been treated *lege artis* i. e. also after the period during which the massive dose is effective.

As regards *the stage at which the massive dose was given*, the figures speak in plainer language. Out of the 82 children (see Table) who had been supplied with vitamin D *within the age of two weeks*, 13 were rachitis-positive, being 16 per cent., whilst out of the 18 who had received the massive dose after that date, 6 showed rachitic changes, making 33 per cent. If the line of demarcation is drawn, instead, at the age of one month, the percentages of the positive cases in these two groups will be found to be 16 % and 57 %, respectively. — Evidently prematures should receive their massive dose at a very early stage.

The mothers were questioned about the children's *infections* during the first year of life. Such enquiries were naturally not concerned with afebrile rhinites, but only with severer infections, such as pharyngo-bronchitis, otitis, diarrhea, pneumonia, tuberculosis, etc. As a rule, the children had managed surprisingly

well to escape infections. The probable explanation is that prematures who catch infections in infancy usually succumb to them, and are therefore scarcely represented at all in this material. Out of 10 children in regard to whom the occurrence of infections was revealed by the anamnesis, no less than 7 showed clinically positive rachitic residues. This is a striking testimony to the bearing of infections on the development of rickets.

No distinctive characteristics in regard to the *social conditions* of the rachitic children could be found in this material.

Voices have been raised in warning against the massive dose treatment, in view of the alleged risk of its injuring certain organs, especially the heart and the blood vessels. But, now that certain toxic products contained in previous preparations of irradiated ergosterin have been eliminated, most investigators consider them, in the usual doses, to be perfectly innocuous. JONSSON-WILTON, in a recent publication, has reported myocardial lesions, in 4 children with reduced vitality of the tissues, treated with a massive dose. His observations, however, obviously cannot be applied out of hand to healthy children. It might a priori be expected that the risk would be considerably greater in the case of prematures. One-fourth of the children comprised in our investigation were therefore examined with the electrocardiograph, but no definite conclusions could be drawn from the results. Nor could any other toxic symptoms, such as vomitings, diarrheas or loss of weight, be observed.

### Summary.

100 prematurely born infants, who had been treated with a massive dose of vitamin D for prophylactic purposes, were subjected to a control examination, in order to ascertain how far they were free from marked rachitic symptoms. This control showed that the protective effect of the administration of 500 000 international units of vitamin D<sub>2</sub> per os was distinctly efficacious. During the three immediately following months the infants, with merely two exceptions, had not received any further supply of vitamin D. In 19 cases slight rachitic residues were clinically

observed. Only 4 of them had been treated *lege artis* after the period, during which the massive dose is effective. Among the said cases, a strikingly large number consisted of twins and of infants who had received their massive dose later than one month after birth. This forces us to the conclusion that the massive dose should be administered at a very early stage, preferably during the first 14 days of life. No definite indications that the massive dose treatment had entailed any toxic lesions could be detected.

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## **Moniliosis of the Respiratory Tract.**

### **(Bronchomoniliosis.)**

By

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In 1845 — a hundred years ago — 189 cases of thrush were treated at the Allmänna Barnhuset in Stockholm. In 139 of these the disease set in during the patients' stay at this institution. Many of these cases developed a serious character and several of the patients died. In 1846, F. T. Berg, M. D., who was the first to hold a professorship in pediatrics in Sweden, published his work on the clinic, pathology and bacteriology of the thrush disease (mycotic stomatitis) a book which still is the most complete, fundamental and comprehensive study on this disease amongst the available books of reference.

Nowadays, the disease termed thrush (monilia infection) is known to the greater majority of Swedish physician merely in the form of a, as a rule, very innocent stomatitis occurring in infants. Generally, it is not considered a serious illness. During the past few years, however, the yeastlike fungi grouped under the name of *Monilia* have stimulated increasing interest as the etiologic factor of a special type of vaginitis occurring in women (Sjöwall).

As regards the thrush disease in infants, the view is now prevalent that it is not a primary disease — at all events not in its more serious forms. It is generally assumed that it arises on the basis of a bad state of health in general, due to disorders of nutrition, deficient hygienic conditions or to some infectious disease. Most physicians consider the possibility of thrush in-

fection developing into any more serious disease in an otherwise healthy and well nourished child unlikely, if not impossible. In addition to a definition of the name bronchomoniliasis and a discussion of the bacteriology, pathology, clinical aspects and therapy of the disease a case of thrush in an infant will be reported in this paper. In this instance the patient, who previously had apparently been in perfect health, was, at the age of 1 month, affected by thrush in the mouth gradually involving such a large area that stenosis of the larynx and risk of suffocation was imminent. Later on — several weeks after the process in the mouth had been arrested — a process developed in the lungs which gradually progressed and which, judging from the circumstances, must have been caused by monilia infection. In this case the diagnosis of bronchomoniliasis was considered as justifiable.

The name bronchomoniliasis has to the author's knowledge not yet been introduced and no broncho-pulmonary form of monilia infection has so far been published in the Swedish literature. In the Anglo-saxon countries, however, this disease has for a long time stimulated increasing interest.

The broncho-pulmonary form of the monilia infection was reported for the first time in 1905 by CASTELLANI, as a disease prevalent amongst natives of Ceylon, employed as »tea-tasters». The disease has since been reported from other tropical countries. Generally speaking, different types of monilia-infection, like infection with fungi in general, seem to be much more prevalent in tropical countries than in temperate zones. CASTELLANI's bronchomoniliasis is, however, known now and has been reported from several countries such as France, England, Greece, Italy and North and South America, and is nowadays recognized to be a nosological entity. Up to 1940, VALADA had established the diagnosis of bronchomycosis in 350 cases of which a large number were cases of bronchomoniliasis. KEIPER stated that out of the cases of diseases of the lungs which came under his observation, 2.93 per cent were caused by Monilia. Literature abounds in publications of cases of bronchomoniliasis. Bronchomoniliasis, therefore, cannot any longer be considered as a rare disease though diagnosis should be established with great care, since the

fungi causing the disease often may occur in the form of a nonpathogenetic saprophyte in the upper respiratory tract, especially in the presence of tuberculosis of the lungs. Mycotic infection, chiefly that localized to the respiratory tract, is much more common than is generally assumed. In cases which resemble tuberculosis of the lungs and in which no bacteria were demonstrable, the possibility of mycotic infection should, therefore, be born in mind.

### *Bacteriology and Serology.*<sup>1</sup>

Moniliae are fungi which resemble yeast, multiply by budding and which, under certain conditions, form micelle filaments. They never form asci or airhyphae. Up to the last decennium, great confusion has prevailed concerning the nomenclature and identification of the different species grouped under the name of Monilia. On the basis of the papers published by HENRICI and, above all, by MARTIN & JONES as well as by YAO and LEE, a systematic classification of the species and proper terminology has of late become possible. The following six organisms are now differentiated; i. e. *Monilia albicans*, *M. parapsilosi*, *M. candida*, *M. Krusei*, *M. mortifera* and *M. stellatoidea*. The specific bacteriological technique for the identification of these fungi cannot be described in detail in this paper. For a more detailed description of this technique the author is referred to the works of the above mentioned authors. Differential diagnosis is generally established on the basis of a study of the aspect of the colonies on various culture media such as Sabouraud's glucose agar and blood agar, further, on the basis of an investigation of the conditions of surface growth on Sabouraud's glucose bouillon, micelle growth on corn flour agar, ability of fermentation of various species of sugar, as well as on the basis of an examination of the morphological structure of the fungi cells. It should be mentioned that in direct specimens from the mouth, throat and

<sup>1</sup> The author's thanks are due to Professor C. KLING for the opportunity offered to him in 1944 of studying at the Bacteriological Laboratories of the State in Huvudsta, methods of isolating and growing the genus *Monilia*.

sputum mycelium is seldom recovered, but chiefly the characteristic, from round to oval shaped yeastlike cells, measuring 2—4 micra in diameter. The mycelium is embedded deep among the epithelium cells, and, as a rule, the specimens or excretions contain only fragments of this organism. On optimum media, such as Sabouraud's glucose agar and Sabouraud's bouillon, mycelium does not grow, and even on meager media such as corn flour agar, certain species form mycelium slowly only and with difficulty. The fungus is Gram positive. S and R forms occur. The morphological structure of the S type is round or oval. The R form presents rather protracted cells.

For the purpose of throwing some light on the pathogenicity of the various geni of *Monilia* for man and experimental animals, a large number of investigations were made (BALOG & GROSSI, MCKINNEY, MICKLE & JONES, CASTELLANI, SCHLATTENBERG & FLINN, MARTIN & JONES, STOVALL & PESSIN, WALLACE & TANNER, IKEDA KANO, KUROTCHIN & LIM, et al.). Moniliasis of the throat and respiratory tract in man, always seems to be caused by *Monilia albicans*. It seems, however, as if the pathogenicity of this genus for experimental animals (and most likely also for man) varies with the different strains. MCKINNEY has made virulence tests on guinea-pigs with 12 different strains from various cases of stomatitis, enteritis and bronchomoniliasis. He injected mixtures of 24 hours cultures subcutaneously, intraperitoneally and intramuscularly into guinea-pigs. 3 of the strains proved fatal for the guinea-pigs, 2 caused abscesses, 3 produced local reaction in the form of swelling, and 4 produced no reaction whatsoever. In rabbits small doses intravenously injected, gave in all instances rise to disseminated nodulated foci, chiefly in the lungs (BALOG & GROSSI). The fungus is markedly pneumotropic when intravenously administered. Administered in large doses it always produced death in rabbits. The post mortem revealed miliary nodulated foci disseminated in the lungs, but they were even found to be present in the spleen and liver. From these foci, *Monilia albicans* could be grown in pure cultures. MARTIN, JONES, CLAUDIUS, YAO & LEE et al. advanced the view that since this organism is capable of eliciting lesions in rabbits,



the assumption is justifiable that it may prove to be pathogenetic for man too. The fact that implantation of the *Monilia* fungus may cause death in man is illustrated by the case of a morphinadict who through neglecting all rules of hygiene and through injecting the drug through his clothing contracted a fatally ending sepsis due to monilia infection.

As was mentioned before, *Monilia albicans* occurs in both S and R forms. MICKLE & JONES demonstrated that the S forms are pathogenetic, while the R forms even in doses of 10 times the strength of the former, are not pathogenetic.

In the attempt of classifying the serological conditions, numerous experiments on animals have been made. Thus, precipitin-, agglutination-, complement fixation reaction- and sensitization- and cutaneous reaction tests have been made by several workers (MICHE, MCKINNEY, STONE & GARROD, MARTIN & JONES, STOVALL & PESSIN, IKEDA KANO, BALOG & GROSSI, MICKLE & JONES, KUROTCHEV & LIM et al.). From the results thus obtained the following can be deduced: *Monilia* forms endotoxins. The diagnostic value of the precipitin reaction in both experimental animal and man manifesting moniliasis, seems to be insignificant. Most authors—among them MICHE—consider the precipitin reaction to be of no value. Better results have been obtained with the agglutination test, but even as regards the value of this reaction opinions differ widely. In general, it is assumed, that the complement fixation reaction test is more reliable (MICHE, STONE & GARROD, MCKINNEY). Regarding the use of the above mentioned reactions for the purpose of identification of the bacteriological types, the prevailing opinion appears to be that the reactions obtained are as regards group or type specificity rather insignificant (MCKINNEY).

BALOG & GROSSI have made experiments with cutaneous reaction tests in cases of pulmonary moniliasis. It appeared that intracutaneous injections of *Monilia* fungi killed by heating, did not cause any local reaction though a general reaction in the form of fever, nausea and headache. They held the view that the toxic effect in this case was not due to a local or general allergic reaction but to toxic substance, i. e. products of decomposition set

free at the death of the fungi. They have also made experiments with intradermal and intracutaneous injections of cultures of living *Monilia*. In patients suffering from bronchomoniliasis, they obtained substantial and distinct »tardy» cutaneous reactions, but no general ill-effects. One case responded with the formation of foci in the lungs and with an impaired general condition as well as with bloody sputum. They maintained that when intra- and subcutaneously administered, even a strongly virulent culture of *Monilia* did not cause any unpleasant ill-effects. They further stated that it was virtually not possible to contaminate the human organism by this way of application. BALLOG & CROSSI, have successfully employed desensitization therapy in a patient suffering from bronchomoniliasis.

#### *Pathology.*

Formerly, it was assumed that the *Monilia* fungus only attacked stratified epithelium (Berg et al.). It has, however, been demonstrated that fungi of various type attacked columnar epithelium and proliferate there. The place of predilection of *Monilia* is, however, the oral mucous membrane and the mucosa of the esophagus. Even the bronchial mucosa may be attacked. On the other hand, however, the lung tissue itself, most likely, is, as a rule, immune against any fungus. Many workers advocated that the *Monilia* fungus in itself was not pathogenetic for man and that it required some primary (irritating) bacterial, toxic or mechanic factor to make it pathogenetic. In this connection the experimental studies made on sensitized rabbits by KUROTSCHKIN and LIM should be recalled. These workers demonstrated on rabbits that intratracheal injection of a culture of *Monilia* did not produce any pulmonary lesions. If, however, the rabbits were first sensitized by means of 3 intravenous injections of a certain dose of a suspension of *Monilia* killed by heating and administered at intervals of 5 days, intratracheal injection of *monilia* culture will give rise to nodulated *monilia* foci in the lungs of the animals. It may be possible that even in man a preceding sensitizing process is involved in the aetiology of

monilia infection of the bronchi and the lungs. But even if sensitization occurs the clinical picture is nevertheless analogous to that of primary monilia infection.

The fungus most likely invades the respiratory organs by attacking the oral mucosa, the pharynx and the upper portion of the esophagus. Direct inspiration of dust containing dried up monilia fungi presumably also plays a part in this process. The monilia fungus is resistant to drying. Direct contamination from individual to individual is also possible. Since the fungus only grows on a sour medium, it should be taken into account that the originally alcalic bronchial mucosa for some reason or other (owing to a primary lesion — mechanical, chemical, bacterial or allergic factors) changes its pH content. Diet may also be a controlling factor in this incidence.

The pathologico-anatomic picture in the experimental animal varies in proportion to the dose of monilia fungus injected administered into the animals. Subsequent to the administration of a strong dose producing at the end of one or two days death in the animal, miliary foci are found in the lungs as well as nodules which microscopically examined show beginning necrosis in the centrum and infiltration of leucocytes at the periphery. If a weaker infective dose was administered and the animal survived for a longer time than reported above, abscess formation was present in the foci as well as epithelioid cells and giant cells (KOERTH, DONALDSON & McCORKLE, IKEDA KANO, et al.). In man, the pathologico-anatomic course and picture seems to be the following: Early fresh, primary lesions due to monilia infection have not yet been described. Most likely, they cannot be differentiated from lesions due to other infections. As was mentioned before, it would seem possible that a bacterial or allergic inflammation of the bronchi or of the pulmonary parenchyma blazes the path for the invasion and growth of Monilia. This is followed by a mild and chronic irritation — inflammation — due to the presence of the fungus in the form of a saprophyte. In such cases the monilia attacks the bronchial walls and lymphatic glands. This seems to be the pathologico-anatomic process underlying bronchomoniliasis in an early stage. The

persistent chronic inflammation encourages fresh infections of various types which cause small broncho-pneumonias, which in their turn foster rapid growth of the fungus. Small abscesses and pseudotubercle arise. In some cases resorption of these small, mycotic tumours takes place, in others they fuse into large foci. On the basis of these two types of abscesses the malign forms of bronchomoniliasis arise. These abscesses may, however heal during the process of fibrosis. All these factors are the aetiological basis of a proliferative process causing pathologico-anatomic changes as, for instance, fibrosis, bronchiectasia, abscesses, atelectasis and emphysema. The microscopic aspect of moniliasis is not marked by any characteristic lesions. There may be presence of nonspecific granulation tissue containing fibroblastic proliferations and cellular exudation. Most frequently, the infiltrate is made up of plasma cells, less frequently, of polymorphonuclears or mixed cellular elements. There also may be presence of peribronchial and perivascular round cell infiltration, proliferative enarteritis and proliferative reactions of the alveolar epithelium. Clearly outlined abscesses surrounded by a broad zone of infiltrate are common. In some areas proliferative changes of the type of interstitial fibrosis predominate obliterating the alveolas and causing atelectasis and emphysema in the adjacent pulmonary tissues. Macrophages as well as foreign body giant cells occur frequently.

In pathologico-anatomic preparations stained by the usual hematoxylin-eosin method, the presence of *Monilia* is not demonstrable. When using the Gram-Weigert method, however, the fungus stains vividly. The yeastlike fungous cells are densely orientated, particularly around the abscesses and in the perivascular lymph space. A micelium is rarely seen.

#### *Clinical Picture.*

Many authors described the clinical picture of bronchomoniliasis in adults (to the author's knowledge no data have as yet been published as to the clinical picture in children). As a rule, the cases are grouped in accordance with their degree of severity

into three different types. Mild, moderate and severe, malign cases. In reality all forms of pulmonary diseases occur, ranging from those which in a high degree simulate advanced tuberculosis of the lungs and acute pneumonia to diseases of a more benign character such as tracheobronchitis, bronchitis and asthma (VADALA, KOERTH, DONALDSON, McCORKLE).

In the presence of a mild form of this disease the patient complains of a slight cough, but does not run any temperature and his general condition is not impaired. The cough may persist for several months. The sputum is scanty, slimy, but not bloody. As a rule, the diagnosis chronic bronchitis is established in cases of this type.

In the cases which are of medium degree of severity the clinical and physical symptoms are more manifest. There may be presence of prolonged subfebrility, of a troublesome cough, of abundant tenacious sputum which even may contain streaks of blood in some instances. As a rule, the diagnosis chronic bronchitis, bronchiectasia or asthma is established. Frequently, pulmonary tuberculosis is suspected.

As regards the severe forms of this disease two types are usually differentiated. One of these is listed as »type of medium degree of severity» which was described above. In a case of this type, the evolution of the disease suddenly takes such a turn that the symptoms suggest acute pneumonia of the lobular or bronchopneumonic type. The patient runs a high temperature and manifests all the clinical symptoms of acute inflammation of the lungs. In the majority of these cases, bacterial mixed infection plays a prominent part in this process. The disease may persist for one week or longer. Frequently, there is complete recovery though empyema or other complications sometimes ensue.

The other type may either develop from the first one, or chronic, progressive and prolonged inflammation may be its underlying cause. The condition closely resembles chronic tuberculosis of the lungs though tubercle bacilli are not demonstrable in the sputum. The disease takes a chronic course marked by exacerbations on one or the other occasion. There is presence of hectic fever, night sweats, loss of weight and weakness. Frequently,

the patient complains of a severe and paroxysmal cough which is most distressing during the night. The sputum is exceedingly abundant, mucopurulent, tenacious, frequently haemorrhagic and has a sweet or yeastlike smell. Not infrequently insufficiency symptoms referable to the right half of the heart are manifested at the last stage of the disease.

In most of the cases roentgen examination reveals signs of chronic bronchitis and bronchiectasia. In severe cases either pneumonic foci or soft, irregular patch-like or streaky shadows as well as peribronchial consolidation are seen in the roentgenograms. Frequently atelectasis and emphysema are visualized. Cavern-like hollow spaces and thickening of the pleura may even occur.

The diagnosis bronchomoniliasis is established on the basis of the clinical picture, of the absence of tubercle bacilli in the sputum and of the evidence of the constant presence of *Monilia albicans* in the sputum. Several authors (BALLOG & GROSSI, MICHEL, STONE & GARROD, MCKINNEY) have advanced the view that cutaneous reaction tests and complement fixation are helpful towards establishing correct diagnosis. When recovering *Monilia* from the sputum and when appreciating the findings great care should be taken. According to KEIPER *Monilia* is found in the cavity of the mouth and the pharynx in 3 per cent of normal and healthy individuals. CASTELLANI insisted on it that when testing of the sputum for *Monilia* is aimed at, the patient should repeatedly rinse his mouth with a sterilizing solution before coughing up sputum. Other workers (VADALA et al.) consider the diagnosis as definitely warranted only on condition that the presence of *Monilia* is demonstrable first in several sputum specimens, and then even in a specimen of secretion directly aspirated through the bronchoscope.

If specimens of sputum are examined for diagnostic purposes, one should proceed in the following manner: 1) Smears of fresh sputum to which 10 per cent NaOH may possibly be added, should be examined. Proceeding in this manner the typical round or oval-shaped fungous cells will be readily visualized even in unstained preparations. In addition, specimens stained by both

Gram's method and by a method for the demonstration of tubercle bacilli should be examined. 2) Cultures from organisms isolated from the sputum should be made on optimal fungus substrate. The most adequate agar for this purpose is Sabouraud's glucose agar. After incubation at 37 C for several days, the characteristic round, raised, yellowish-white, shiny and pasty colonies smelling typically like yeast are easily differentiated. Since other more or less pathogenetic fungi (for instance actinomyces, coccidioides, sporotrichum, aspergillus) which grow rather slowly on Sabouraud's medium are in some instances found in the sputum the cultures should be observed over a period of two weeks (GILL). After isolation of the fungus from Sabouraud's medium, the bacteriologic identification should be made in accordance with the previously indicated instructions. Since it seems to be now generally recognized that of all the reported parasitic fungi the genus *Monilia albicans* alone is pathogenetic for man it is from the diagnostical point of view important that the identification and classification of the organisms into their species is made by a bacteriologist in every individual case.

For therapeutic purposes the following methods of treatment have been used: 1) treatment with large doses of natrium iodid and potassium iodide administered per os possibly coupled with intravenous injections of potassium iodide. A course of this treatment should extend over a period of at least a few weeks. 2) The administration of methylene blue per os or intravenously. In adults and if administered per os, 10 to 20 mg of methylene blue should be given four to five times a day. This drug is available in the form of pills of gelatine. If injected intravenously, 1 to 2 cc of a sterile 5 per cent solution is given per day. 3) The administration per os of 1 per cent gentian violet solution in doses of 5 to 8 mg per body weight, or 5 mg per body weight in 3 to 4 cc physiologic NaCl administered intravenously. (This, however, incurs risk of thrombosis. Administered extravascularly it causes necrosis.) 4) The intratracheal or intramuscular administration of lipiodol. 5) Vaccine therapy. 6) Roentgentherapy.



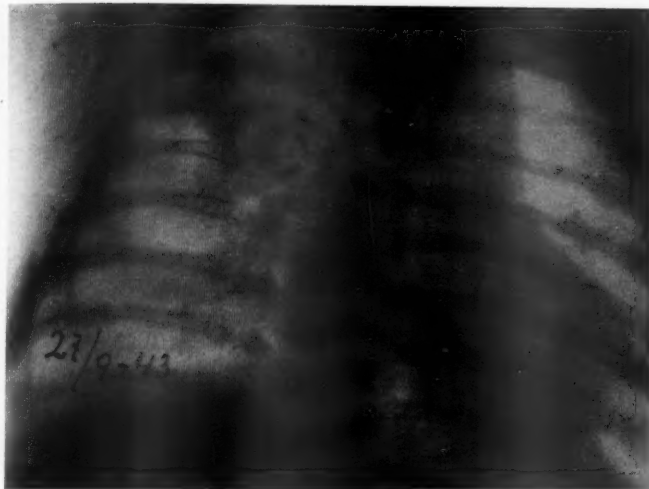


Fig. 1.

*Report of a Case of Bronchomoniliasis in an Infant.*

Record no 199/1943, a boy, H. L. born on July 27, 1943. On September 2, 1943, he was admitted to the Department for Children of the Military Hospital in Boden. The mother had a normal delivery and the after-course was uneventful. Birth weight 3100 g. He was breast-fed for some weeks. Breast-milk diet was discontinued because of the mother developing an abscess on the breast. He was fed on the following formula: 2 coffee-cups of milk, 2 coffee-cups of water and 2 table-spoons of sugar (C:a 6.5 per cent sugar). Previously, the boy had been in good health. 9 days prior to his admission to the hospital, whitish spots (thrush vegetation) developed on the tongue and on the palate which increased in size from day to day. On the last day before he came to hospital, difficulty of breathing set in, and he could not take in any food. As the bowel movements had been rather slow during the past few days, his mother gave him in the morning of September 2, the day of his admission to the hospital, 2 tea-spoons of castor oil which had a »satisfactory effect». On September 2, in the afternoons and in the evening, the baby had repeatedly turned blue in the face and had gasped for breath. For this reason the district physician referred him in the



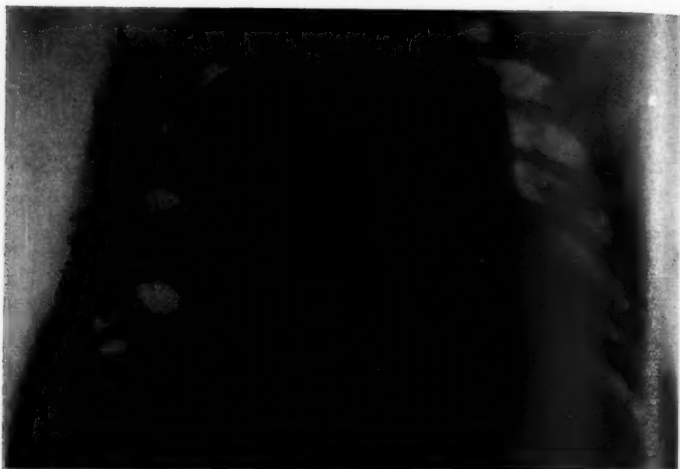


Fig. 2.

evening to the hospital. The mother denied having had any vaginal discharge.

On September 9, at 10 o'clock p.m. the examination of the patient revealed the following conditions: A well-shaped and well-fed baby boy. Turgor and tonus were slightly impaired. There was distinct labored breathing which was partly stridulous and accompanied by movements of the nostrils and circumoral cyanosis. There was absence of exanthema and bleeding. As regards the skull, fontanelle and the remaining skeleton there was nothing of note. Temperature: 37.3 C. Weight: 4100 g.

*Pharynx:* The entire pharynx — the tongue, the inside of the cheeks, the hard and soft palate, the posterior walls of the pharynx, as far as one could see — were coated with thick yellowish-white thrush vegetations which most likely extended deep down into the throat. Even the lips, as far as to the level of the red of the lips, were coated with thrush vegetation. *The lymphatic glands* were normal. *Lungs:* There was absence of dulness. The respiratory sound was stridulous but otherwise normal. There were no râles. *Heart:* The heart was not enlarged. The sounds were clear. There were no murmurs. *Abdomen:* The abdomen was soft, and there was no tenderness. The liver and spleen were not palpable. *Reflexes:* As regards the pupillary, patellar reflexes and Achilles tendon reflex there was nothing of note. *Pharynx tests:* On the specimens from the pharynx cocci were grown, but the tests were ne-



Fig. 3.

gative for diptheria bacilli. *Blood count*: Hemoglobin 71 per cent, red blood cells 3 320 000, white blood cells 6 000. The differential count findings were: staff cells 19 per cent, segmented cells 27.5 per cent, eosinophils 1 per cent, lymphocytes 52.5 per cent, monocytes 0 per cent. *Urine*: Heller-Almén-Sediment: Nothing pathological was found. Alcalic reaction. *Micro sedimentation rate*: 18 mm per hour. The *Wassermann reaction* was negative. On September 3, roentgen examination of the lungs revealed normal conditions.

*Evolution*. Oxygene was administered with the patient in dorsal elevated position. The infant was fed on Ringer's solution. Locally the thrush was treated by applying a 0.20 per cent solution of gentian violet to the involved area. Already a few hours subsequent to this treatment the thrush vegetation on the lips and in the mouth came off in large sheets. Slight difficulty in breathing, however, persisted.

September 4: Respiration had become normal. Absence of thrush vegetation in the throat and the pharynx. Temperature was elevated. The patient developed a cough. *Lungs*: Posteriorly on the right, slight râles were heard over several areas. Sulfathiazole in doses of 0.1 g was administered 5 times a day.

September 8: Temperature was normal. The general condition of the patient was satisfactory. Reappearance of a few white spots in the mouth which were locally treated in the reported manner.



Fig. 4.

September 15: Temperature rose again. The micro sedimentation rate was 67 mm per hour. Blood count finding: White blood cells 24 000. Sulfathiazole was again administered. Physical examination of the lungs did not reveal anything definite. There were no thrush vegetations.

September 18: Roentgen examination revealed bilateral bronchopneumonic consolidation.

From this day onwards the disease developed as follows: Until October 20, subfebrile periods alternated with periods of fever. From then on the patient was afebrile. Throughout the whole time his general condition had been satisfactory, and seemed to be completely unaffected. Since September 9, he had continuously put on weight. The gradual development of bilateral parenchymal processes was visualized in the roentgenograms. On October 10, these attained their maximum expansion. From then onwards, consolidation gradually regressed, and on January 15, it had almost completely disappeared (See Fig. 1—6).

On October 6, and October 15, the gastric contents were removed and Sabouraud's agar was inoculated with specimens thus obtained, partly in the laboratories of the hospital and partly in the Bacteriologic Laboratories of the State. The growth of *Monilia albicans* was obtained.

From October 3 to October 9, the temperature was elevated. There



Fig. 5.

were loose, minced and bloody stools 2 to 3 times a day. On October 5, specimens from the stools were sent to the Bacteriologic Laboratories of the State. Growth of *Monilia albicans* was demonstrated. There was no growth of *Salmonella* or *Bacteria dysenteriae*. On October 8, the stools were again tested for *Monilia albicans* with a positive result.

From September 14 on, there was no trace of thrush vegetation in the mouth or pharynx. Tuberculin test (Mantoux up to 1 mg was the whole time negative). The micro sedimentation rate was about 60 mm per hour. From November 11, sedimentation rate slowed down and on January 15, 1944, it returned to normal values.

From September 16, sulfathiazole was constantly administered in large doses though without any effect. The bronchopneumonic foci continued to expand. On October 11, treatment with potassium iodide in doses of 0.15 g four times a day was instituted. On October 30, this dose was increased to 0.20 g and administered 6 times a day. This treatment was continued until November 16, the date when the patient was discharged from hospital. At that time, the patient's weight was 5400 g. Treatment with potassium iodide in doses of 0.10 g + sodium iodide in doses of 0.10 g, 3 times a day was continued after the patient's discharge from hospital. On January 15, the control examination of the lungs showed normal conditions and the treatment was discontinued. On February 2,



Fig. 6.

1945, when examined again, the child was in excellent condition. The examination of the lungs did not reveal anything of note.

*Epicrisis.* Infant aged 5 weeks, a well-fed male who had chiefly been given artificial diet, and who was apparently well cared for developed thrush vegetation in the mouth and in the pharynx. On the 9th day of the disease, he manifested symptoms of suffocation which endangered his life. He was therefore taken to hospital. At the end of only a few days' treatment with 0.2 per cent of gentia violet dilution, fasting and intake of liquids, the thrush vegetation disappeared and difficulty in breathing subsided. Two weeks later the patient developed a cough and ran a temperature. The roentgen examination revealed bilateral bronchopneumonic foci. The pulmonary lesions gradually expanded in spite of treatment with sulfathiazole. Treatment with potassium iodide per os checked the process. It gradually subsided and finally disappeared completely. It had persisted for four months. Throughout the whole course of the disease, the general condition of the patient was surprisingly good. He even put on weight.

The growth of *Monilia albicans* on cultures from the patient's gastric contents was repeatedly demonstrated. Likewise, repeated tests of the stools for *Monilia albicans* gave positive results. Throughout the entire course of the pulmonary disease there were no thrush vegetations in the mouth or in the throat.

The antecedents, the clinical course, the roentgenograms and the obvious therapeutical effect of potassium iodide strongly supported the diagnosis of bronchomoniliasis in this case. The findings of *Monilia albicans* in the gastric contents are, of course, not conclusive — the possibility that thrush vegetation or thrush fungi which are present in the pharynx or esophagus might be admixed to the test specimens cannot be definitely excluded. Viewed in the light of the evolution of the disease, and of the clinical picture in general, it may, however, be said, that the findings in the reported case, warranted, at least to a certain extent, the diagnosis of bronchomoniliasis.

### Summary.

On the basis of a careful study of the literature, the author describes the conditions termed bronchomoniliasis, discusses the bacteriology, pathology, clinical picture and methods of treatment of this disease, and reports a case of bronchomoniliasis in an infant that came under his own observation.

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## **Chemo-prophylaxis against Nosocomial Infections.**

By

**YNGVE LARSSON.**

The nosocomial infections have always formed one of the main problems with regard to the hospital treatment of children. At the first children's hospitals, founded in the beginning of the nineteenth century, the frequency of infection is said to have equalled almost 100 per cent, the mortality rate being 80—90 per cent. However, the frequency of nosocomial infections is still high. This was established f. i. at the Northern Pediatric Congress in Stockholm in the year 1934, where the main theme of the discussion concerned the nosocomial infections. Thus, the frequency of infection at the children's hospital in Oslo was approximately 50 per cent (FRÖLICH), being 40 per cent in Copenhagen (POULSEN) and about 30 per cent at Kronprinsessan Lovisas Hospital for Children in Stockholm (LICHTENSTEIN, PERMAN). The frequency is likely to have been reduced somewhat during the last ten years. However, a very high frequency of infection must still be taken into account. Formerly, the nosocomial infections mostly comprised the common epidemic childhood diseases, whereas nowadays the acute infections in the upper respiratory tract and their complications (otitis, sinusitis, bronchitis, pneumonia, dyspepsia, etc.) constitute the principal manifestations of these infections.

Hitherto, the campaign against the nosocomial infections has, on the whole, followed two lines, viz., firstly, an exposition prophylaxis which implies, among other things, appropriate accommodation with good facilities for isolation and a very strict



discipline among the staff with regard to infection risks and, secondly, a predisposition prophylaxis with a view to improving the individual power of resistance by ample food and open air treatment, etc. In the latter instance, more specific measures have also been adopted, such as anti-measles or anti-diphtheria immunization, pertussis-vaccination or attempts at so-called anticatarrh vaccines. However, opinions differ concerning the merits of the last-mentioned method.

At the Kronprinsessan Lovisas Children's Hospital, the effect of the above-mentioned prophylactic measures with regard to infection has not been particularly marked. This is, above all, due to the out of date accommodation, with a considerable lack of isolation and quarantine departments. In January 1944 the nosocomial infections appeared to become exceptionally frequent. The idea was then conceived of attempting to prevent these infections by means of a continuous administration of small doses of some sulfanilamide compound. However, several investigators have advised caution against such a *chemo-prophylaxis*. Thus, BEAUMONT and DODDS state quite categorically, in the latest, edition of *Recent Advances in Medicine*, as follows: »The prophylactic administration of small doses of sulphanilamide against various types of infection, such as sore throats or colds, is useless.» Further, in an Editorial in the *Lancet* of the year 1940 regarding »The common cold», the increasing habit of prescribing sulfanilamides in the case of upper respiratory infections, which are not due to streptococcal or pneumococcal infection, is criticized. Similar warnings have been expressed in Sweden by, among others, INGVAR and LÖFSTRÖM.

However, a perusal of available literature shows that the sulfanilamides have already been tested as a prophylactic medium in several different quarters with, as a rule, encouraging results. Some of these earlier experiments will be recorded here. — To begin with, the use of chemo-prophylaxis with small doses of sulfanilamides finds support in experimental examinations. Thus, FLEMING, among others, has shown that the bacteriostatic effect *in vitro* is evident even in dilutions corresponding to a blood concentration of approximately 1 mg % and less. However, they

point out, what seems to be quite natural, that the bacteriostasis is inversely proportional to the quantity of inoculated bacteria. The preparations have a prophylactic effect also in animal experiments. This effect has been studied by RICHTNÉR, among others. He was in a position to establish »an excellent prophylactic effect» in experimental rhinitis and sinusitis in rabbits.

The chemo-prophylaxis has been clinically tested in the following disease conditions. In the case of *wound injuries* of different kinds and especially in war injuries, BUTTLE and FULLER-JAMES, and others, recommend the use of sulfa-compounds as a prophylaxis, by mouth as well as locally. They succeeded to a great extent in preventing infection by aerobic as well as anaerobic bacteria owing to the administration of a small continuous sulfa dose for a period of 2 weeks, giving a blood concentration of approximately 3 mg %. When an infection was observed, this notwithstanding, it could generally be checked by increasing the drug to the size of a therapeutic dose.

Furthermore, sulfanilamide as a prophylaxis has been tested in *obstetrics* with regard to puerperal infections. Thus, during a whole year, JOHNSTONE administered this drug to all the newly delivered women for a week after the parturition at the clinic in Edinburgh. He was able to ascertain a decrease in the severe cases of puerperal sepsis from 3.5 per cent to 1.9 per cent. COLEBROOK recommends chemo-prophylaxis in practical obstetrics in all cases incubated with hemolytic streptococci, or whenever the risk of infection is evident.

In cases of *scarlet fever*, STRÖM at the hospital for infectious diseases in Stockholm and SAKO & collaborators in Minneapolis used sulfanilamide as a prophylaxis against complications. Both employed a small continuous dose. Ström administered this dose throughout the disease, while Sako only used it during the first 12 days. A statistically significant reduction in the frequency of complications was obtained in both cases with but one difference, viz., Ström found that only the purulent complications decreased, while Sako considered himself able to prove that also the toxic complications and especially the nephritic cases were considerably more scarce.

In *measles* and *whooping cough* THOMPSON and GREENFIELD similarly administered prontosil as a prophylaxis against complications. Thus, 400 out of 1 219 cases of measles were given this drug during the whole time of hospital stay, while 819 cases represented a control material. The effect obtained was quite distinct. Thus, among the treated cases, 1.7 per cent were subjected to broncho-pneumonia and 2.9 per cent to otitis, while the cases not treated fell ill in pneumonia in 4.8 per cent and otitis in 11.8 per cent, in spite of the fact that, at the admission to the hospital, the treated group comprised the more severe cases. On the other hand, the result was not equally marked in the cases of whooping cough. When a complication occurred in spite of the prophylaxis, it could easily be checked by an increase in the dose to a therapeutical quantity.

LONG and BLISS give an account of a milk-borne epidemic of *streptococcal angina* which was quickly arrested by means of preventive chemo-therapy. SMITH, however, was unable to produce an effect on a tonsillitis epidemic in an analogous way.

In *upper respiratory infections*, LÖFSTRÖM has administered sulfapyridine in order to prevent bacterial complications when suspected of being imminent. This caused a fall in the frequency of the complications from 18.4 per cent in the control material to 5.9 per cent among the treated cases.

As regards an epidemic of *meningococcal meningitis* in the year 1943 at a large American military camp, chemo-prophylaxis with sulfadiazine, i. e. sulfadimine, was tried by KUHN, and others. Half the force, 15 000 men, were given the drug during 3 days, while the other half, 18 800 men, was not treated. After this, only 2 new cases of meningitis occurred among those treated, whereas 40 appeared in the control group.

Further, interesting examinations have been performed by COBURN-MOORE and THOMAS-FRANCE-REICHSMAN with the prophylactic administration of sulfanilamide to patients susceptible to *rheumatic fever*. The intention was to prevent hemolytic streptococcal infections on account of their known deleterious influence on the rheumatic disease. Accordingly, during a 4-year-period, Thomas gave a small dose of sulfanilamide each winter from

October to June to 55 individuals, most of whom were 14—19 years old and who had earlier undergone one or several rheumatic attacks. The blood-concentration was maintained at about 2 mg %. 67 other patients with the same disease acted as a control material. The patients were subjected to ambulant control every third week. 2 mild rheumatic relapses occurred among the treated cases, while, in the control material, 15 severe rheumatic fevers, 6 milder rheumatic attacks and 5 (possibly 9) uncertain cases with more diffuse rheumatic symptoms without fever were noted. In the control group, 4 patients died, 2 of endocarditis, while all the treated patients survived. Thus, the results were very favourable, only the material is rather small. Coburn treated 80 rheumatic children from New York in an analogous way and obtained the same preventive effect with regard to relapses. However, there was no control material in his investigation.

FANCONI in Zürich performed a test with chemo-prophylaxis closely resembling our own examination. At a small children's sanatorium under the direction of Fanconi, the *nosocomial infections* were extremely troublesome during a comparatively long time, wandering from child to child without intermission. Then, for a period of 3 weeks, all the children were given sulfathiazole in a fairly small dose. During this time the infection disappeared completely, the children's temperature dropped to normal and their sedimentation rates decreased. Nor did the infection return when the administration of the drug ceased. However, a control material is lacking in this case, too.

The most comprehensive and important investigation regarding this subject remains to be mentioned, viz., the extensive experiments with mass chemo-prophylaxis which have quite recently been performed in the United States Navy, — later than any of the above-mentioned investigations and simultaneously with the author's own. COBURN organized these investigations. The purpose in view was to reduce the streptococcal morbidity and lessen the frequency of respiratory infections, scarlet fever epidemics and rheumatic infections, which at times very seriously affected the fighting ability at the time of the mobilization, when a great number of young individuals liable to infections were moved to strange

surroundings rich in bacteria. Thus, for 4-6 months approximately 600 000 recruits obtained a daily dose of 1 Gm. of sulfadimine. Immediately a considerable decrease occurred in the frequency of all the more simple upper respiratory infections as well of their complications, scarlet fever and the rheumatic infections. As regards an equally large, not treated control material, the difference in the frequency of infection was, without any doubt whatsoever, statistically significant. The concentration of the drug in the blood was maintained at about 2 mg %. Toxic effects appeared in 0.5 per cent, the majority of them being in the shape of benign rashes. Serious toxic reactions were found in only 0.01 per cent, viz., exfoliative dermatitis and granulocytopenia. 12 deaths were recorded in complications of this type. No sulfanilamide-resistant strains of bacteria appeared during the investigation. In summarizing, Coburn states, regarding the results, as follows: »One cannot estimate accurately the saving in dollars, man-days or lives which results from chemo-prophylaxis.»

Thus, the results of earlier experiments with chemo-prophylaxis have been rather favourable. We therefore couldn't find any important objections to a trial with a sulfanilamide compound for preventing the nosocomial infections at Kronprinsessan Lovisas Children's Hospital. Such a chemo-prophylaxis was, in fact, tested, and an account will be given below of this experiment.

#### *Own Investigation.*

The investigation lasted for 4 months during the period  $\frac{17}{1}$ — $\frac{17}{6}$  of the year 1944, i. e. during a time of the year when nosocomial infections are generally, according to experience, severe and persistent. By kind courtesy of Dr HINDMARSH, access was given to the patient material at the surgical department of the hospital. A sufficiently large number of cases during the given time was thereby made available for statistical analysis. Among the patients admitted to the hospital during this period, and not disclosing any signs of infection or fever on admission, every other one was administered sulfathiazole as a prophylaxis, while the remaining cases of the same kind represented the control material.

Table I.

## Dosage.

Initial dose 0.025 gm sulfathiazole per kg of body weight  
 Then 3 (4) times daily 0.012 » » » » » » » »

Age	Prophylaxis		Therapy	
	Initial dose	Then 3 (4) times daily	Initial dose	Then 5 times daily
1-6 months	0.15 gm	0.10 gm	0.25 gm	0.12 gm
6 m.-2 yrs.	0.30 »	0.15 »	0.50 »	0.25 »
2-6 yrs.	0.50 »	0.25 »	1.00 »	0.50 »
6-10 yrs.	0.75 »	0.50 »	1.50 »	0.75 »
10-14 yrs.	1.00 »	0.50 »	2.00 »	1.00 »

Sulfathiazole was selected, partly for practical reasons, since it was to be had in tablets of only 0.2 Gm. and, partly, because it was considered suitable in this investigation to use a drug other than the one administered as a matter of routine at the clinic in chemotherapy, viz., at present sulfadimine.

The drug was given by mouth continuously during the whole of the patient's stay at the hospital. The dosage was calculated to maintain a concentration in the blood of about 2-3 mg %, i. e. hardly half the concentration usually occurring in sulfanilamide treatment. The initial dose was made somewhat larger than the subsequent ones. Accordingly, 0.025 Gm. per body-weight was administered initially, then 0.012 Gm. per body-weight three and, later, four times daily. For practical reasons, a dosing scheme was arranged on the basis of the above-mentioned factors, which may be seen in Table I. The white blood cells were counted twice a week and the urinary sediment was examined once a week in the treated patients. In addition, the sulfathiazole level in the blood was determined every other day in these patients. For this, MARSHALL's micromethod, modified by FRISK, was employed. In all, 1 089 determinations of this kind were performed and the result may be derived from Figure I. The blood tests were carried out in the morning before the patient had received the first tablet

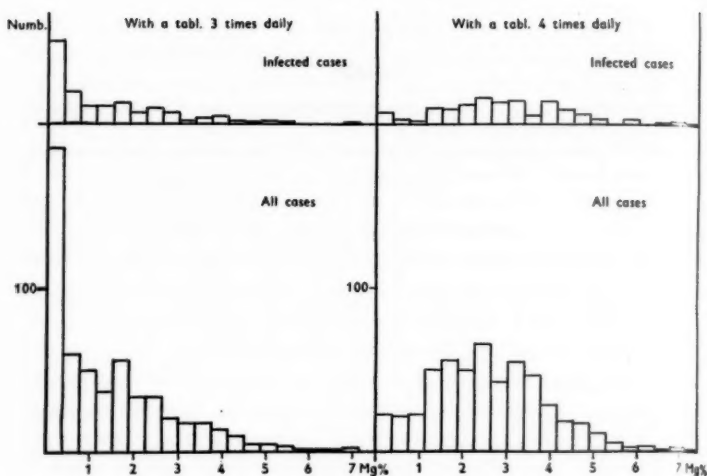


Fig. I. The concentration in the blood.

for the day. These tests showed that in approximately one third no sulfathiazole whatsoever was ascertainable. This is, of course, due to the excretion of the whole quantity, administered on the preceding day, during the night. For the purpose of counteracting this rapid excretion, the number of tablets was increased after a couple of months to 4, instead of 3, every twenty-four hours. As will be noted in the figure, the concentration then kept at about 2—3 mg % even during the night. The Fig. I will also serve to indicate that the concentration, in the cases affected by nosocomial infections in spite of the prophylaxis, did not in any way deviate from the concentration in the total material. Nor was any difference in the frequency of infection observed before and after the increase in the dosage (19 infections before and 14 afterwards).

The material comprises a total of 600 children, 291 of which were treated, 309 representing not treated control cases. However, the drug had to be withheld in 42 instances for reasons which will be entered upon below. These 42 cases have been regarded as new ones after the discontinuation of the drug and referred to the

Table II.

The total material.

	Surg. dep.	Med. dep.	Total
Treated cases . . . . .	161	130	291
Not treated cases . . . . .	211	140	351
Total	372	270	642

Table III.

The age distribution.

Age in yrs.	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	>10
Treated cases	61	34	29	22	17	24	16	17	21	12	38
Not treated cases	87	32	47	18	20	24	20	17	16	11	59

Table IV.

The frequency of infection.

		A. Treated cases	B. Not treated cases	Difference $A - B \pm \epsilon (D)$
Med. dep.	Uninfected cases	113	108	—
	Infected cases	17	32	—
	% infected cases	13.1	22.9	$9.8 \pm 4.6$
Surg. dep.	Uninfected cases	145	163	—
	Infected cases	16	48	—
	% infected cases	9.9	22.7	$12.8 \pm 3.7$
Total	Uninfected cases	258	271	—
	Infected cases	33	80	—
	% infected cases	11.3	22.8	$11.5 \pm 2.9$

control group. The material consequently consists of 642 cases (Table II). The age distribution is recorded in Table III.

The result is illustrated in Table IV, where the total frequency of infection will be seen to have been considerably higher among



Table V.

The total number of infections.

		Numb. of times infected						Total cases	Total infections	% infections	Difference $\pm \epsilon (D)$
		0	1	2	3	4	5				
Med. dep.	Treated	113	16	1	—	—	—	130	18	13.8	$24.0 \pm 5.1$
	Not treated	108	20	5	6	—	1	140	53	37.8	
Surg. dep.	Treated	145	16	—	—	—	—	161	16	9.9	$15.7 \pm 3.9$
	Not treated	163	43	4	1	—	—	211	54	25.6	
All cases	Treated	258	32	1	—	—	—	291	34	11.7	$18.8 \pm 3.1$
	Not treated	271	63	9	7	—	1	351	107	30.5	
Total		529	95	10	7	—	1	642	141	21.9	

the patients not treated, and the difference is statistically significant.<sup>1</sup> However, these figures only denote the number of patients who contracted infection. The real frequency figure with regard to infection lies considerably higher owing to the fact that many children, those in the control material in particular, fell ill in nosocomial infections several times. Table V illustrates the situation with regard to these repeated infections, showing still greater differences as between the two groups of patients.

Nevertheless, this difference is not necessarily the result only of the chemo-prophylaxis, as the patients in the control material had, on an average, a longer hospital stay than the treated patients, and it is known from an earlier investigation (LICHTENSTEIN) that the longer the stay at the hospital the greater the risk of nosocomial infection. Thus, the number of days at the hospital per patient is 9.1 in the treated group and 16.8 in the control group. This difference is partly due to the fact that the patients in the control group have had to remain for a longer period at the hospital on account of the greater number of infections, but the

<sup>1</sup> I am indebted to Professor GERT BONNIER at Stockholms Högskola (The University of Stockholm) for valuable suggestions with regard to the analysis of the statistical material.

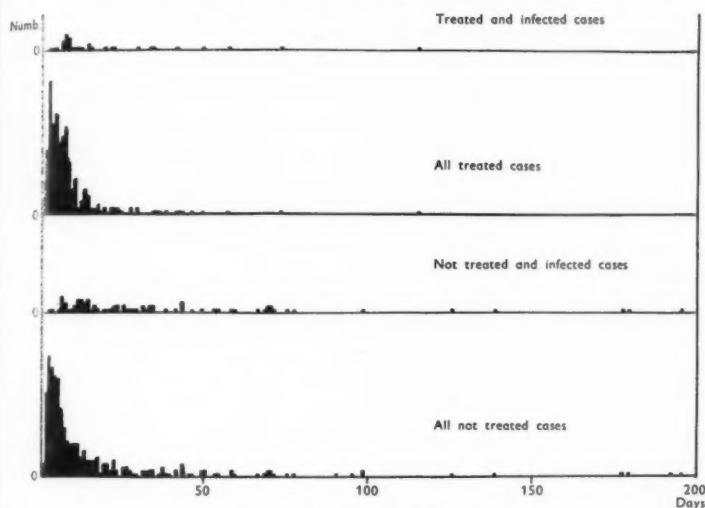


Fig. II. Time of hospital stay.

difference may, to a certain extent, also have occurred quite by chance (Figure II). However, when the material is reduced by the exclusion of cases with a hospital stay exceeding 35 days, the difference in the number of hospital days per patient is equalized, being 7.5 in the sulfathiazole group and 9.0 in the control group. In a comparison of the frequency of infection in the thus reduced material, a statistically significant difference is still evident between the two series (Table VI). No other reason for this difference than that of the prophylactic sulfathiazole administration exists.

The type of infection in the two groups is classified in Table VII. As will be observed, there is no particularly marked qualitative difference between them. On the other hand, when the infections are grouped according to their duration and maximum temperature, the infections in the sulfathiazole group are found to be, as a rule, more benign than those in the control group. This will be evident from Figures III and IV. The difference as regards the conditions of temperature is, however, statistically uncertain.

Table VI.

The frequency of infection in the reduced material.

	Total material		Reduced material (Hospital stay < 35 days)	
	Treated	Control	Treated	Control
Uninfected. . . .	258	271	253	255
Infections . . . .	34	107	29	60
% infections . . .	11.7	30.5	10.3	19.4
Diff. $\pm \epsilon(D)$ . . .	18.8 $\pm$ 3.1		9.1 $\pm$ 2.9	
Hospital days per patient . . . .	9.1	16.8	7.5	9.0

Table VII.

The type of infections.

	Treated	Not treated
Cold without fever . . . . .	6	12
Pharyngitis . . . . .	15	55
Dyspepsia . . . . .	5	17
Pneumonia, capillary bronchitis . . . . .	3	3
Angina tonsillaris . . . . .	3	8
Otitis media . . . . .	1	5
Urinary tract infection . . . . .	—	1
Bronchitis . . . . .	—	4
Cholera infantum . . . . .	—	1
Erysipelas . . . . .	—	1
Uncertain infection . . . . .	1	—
	Total 34	107
In addition:		
Measles . . . . .	6	6
Scarlet fever . . . . .	1	4

(These cases were not included, when the frequency of infection was calculated.)

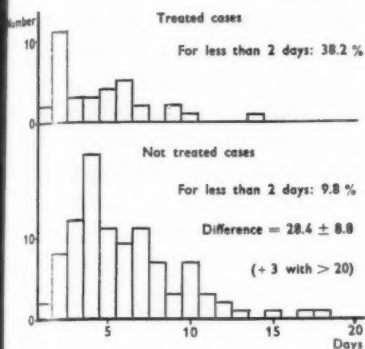


Fig. III. The duration of the infections.

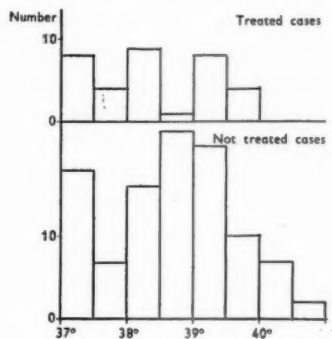


Fig. IV. Maximum temperature.

Treated cases:  $> 38.5^{\circ}$ : 38.8 %  
 Not treated cases:  $> 38.5^{\circ}$ : 61.8 %  
 Difference:  $= 23.5 \pm 9.5$

The infections have required chemo-therapy 10 times in the control cases, and twice in the treated cases. Three patients died of the infection, 2 in the control group and 1 in the sulfathiazole group, being one case of mongolism with a severe congenital heart lesion, one case of atresia intestinalis and one case of megacolon. Thus these cases concerned children whose power of resistance was greatly reduced by another disease.

As to the toxic manifestations of the drug it has already been mentioned that the administration of the drug had to be withheld in 42 instances. Only in 18 of these cases the discontinuation of the prophylaxis may be connected with the sulfathiazole medication. These cases are recorded in Table VIII, from which it

Table VIII.

## Toxic reactions.

Toxic reactions.	Number
Leucopenia (lowest value 2 700) . . . . .	5
(No granulocytopenia)	
Microscopical hematuria . . . . .	2
Abundant sulf crystals in urinary sediment . . . . .	1
Vomiting without other known cause . . . . .	7
Drug fever(?) . . . . .	3
Total	18

Table VI.

The frequency of infection in the reduced material.

	Total material		Reduced material (Hospital stay < 35 days)	
	Treated	Control	Treated	Control
Uninfected. . . .	258	271	253	255
Infections . . . .	34	107	29	60
% infections . . .	11.7	30.5	10.3	19.4
Diff. $\pm \epsilon (D)$ . . .	18.8 $\pm$ 3.1		9.1 $\pm$ 2.9	
Hospital days per patient . . . .	9.1	16.8	7.5	9.0

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Urinary tract infection . . . . .	—	1
Bronchitis . . . . .	—	4
Cholera infantum . . . . .	—	1
Erysipelas . . . . .	—	1
Uncertain infection . . . . .	1	—
	Total 34	107
In addition:		
Measles . . . . .	6	6
Scarlet fever . . . . .	1	4

(These cases were not included, when the frequency of infection was calculated.)

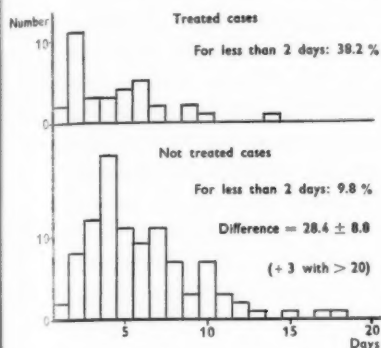


Fig. III. The duration of the infections.

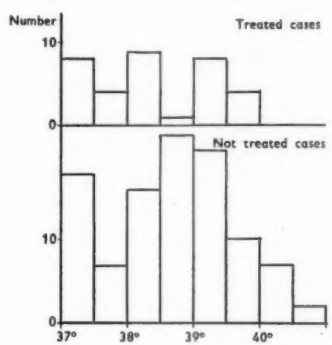


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Table VIII.

Toxic reactions.	Number
Leucopenia (lowest value 2700) . . . . .	5
(No granulocytopenia)	
Microscopical hematuria . . . . .	2
Abundant sulf crystals in urinary sediment . . . . .	1
Vomiting without other known cause . . . . .	7
Drug fever(?) . . . . .	3
Total	18

will be seen that no severe toxic reactions occurred. As regards the remaining 24 cases, the cause of the discontinued dosage had no reference to the sulfathiazole. In some of these cases the drug was withheld on account of doubtful surgical indications with regard to acute abdominal cases, so as not to conceal the course of the disease. In other cases it concerned children suffering from congenital pyloric stenosis, coeliac disease, etc. who were unable to benefit from the prophylaxis owing to the vomiting. In yet some cases the treatment was interrupted by mistake owing to the moving of the patient from one department to another.

### *Comment.*

It is evident that this investigation has produced positive results, similar to earlier chemo-prophylactic experiments with sulfanilamide compounds. Before discussing its practical consequences, a brief account of possible risks which may be involved in a more generally performed chemo-prophylaxis seems justified. The following factors should be observed in this connection:

1. The toxicity of the drugs. Considering the at times fatal injuries which may ensue from the administration of sulfanilamides, it is a common opinion that they should be reserved for cases with clear and urgent indications. However, serious toxic reactions are, as a rule, only noticed after a maximum administration of the drugs. Further, HERBERTS has recently demonstrated that the toxicity is lower in healthy individuals than in those already subjected to infection.

2. The risk of a chemo-resistance. It is a well-known fact that the bacteria can develop a resistance towards the sulfanilamides. However, it is equally clear that before the onset of an infection no bacteria occur which might become chemo-resistant, at least not bacteria other than those normally to be found in the non-pathogenic flora of the throat. On the other hand, when the patient has become infected with a pathogenic agent, it is probable, or at any rate conceivable, that the comparatively low concentration of the sulfa-drug may suffice to check the infection during the incubation period, before the bacteria have had time

to grow to any greater quantity. Experiments *in vitro* favour this conception. However, if the infection is massive, it will, perhaps, overcome the sulfa-effect and cause manifest symptoms. In such an event, the drug should either be altogether withheld immediately or the dose increased to full therapeutical strength, on account of the apparently common experience that the infections which get inadequate initial doses, later may become refractory towards treatment.

3. A third factor concerns the etiology of the acute upper respiratory infections. Often it is a question of virus infections, on which sulfanilamides have no effect. However, a bacterial infection occurs almost without exception simultaneously or secondarily in children. If it should prove impossible to check the primary virus infection, chemo-prophylaxis should, nevertheless, be capable of preventing the often more serious bacterial complications. This has been established in a work by CECIL, PLUMMER, and SMILLIE who administered sulfadiazine in common cases of upper respiratory infections. They were in a position to ascertain a reduction in the number of secondary infections as well as a decrease in the nasopharyngeal bacterial flora as compared with a group of not treated control cases.

4. Sometimes the use of these drugs is advised against in mild respiratory infections, since the immunization process following every such infection would then be lost. However, no support for this conception has been offered. On the contrary, the antibody formation has been shown to be the same with and without chemotherapy (FINLAND-BROWN, GREGG-HAMBURGER-LOOSLI, WHITBY, GREEN).

5. Finally, a risk is naturally inherent in the fact that the patient might be sensitized towards the drug during the prophylaxis. This risk cannot be ignored, but there is always a possibility of trying another compound within or without the group of sulfanilamides in the event of an infection in a patient having become hypersensitive to the drug.

Thus, the risks of chemo-prophylaxis should not be exaggerated. Further, considering the established value of the prophylaxis as a protection against infection, the question of



extending its use should be seriously examined. In isolated groups of children threatened by infection, as in some children's homes, in refugee camps, etc., a chemo-prophylaxis, under careful control and perhaps with somewhat smaller doses than the ones given here, should undoubtedly be of great value, at least at times when the risk of infection is particularly pronounced. Besides, such a test of chemo-prophylaxis would facilitate further studies of the advantages and possible risks inherent in the method.

### Summary.

1. Earlier experiments with chemo-prophylaxis indicate the definite value of this method as a protection against infections of various kinds.
2. Experiments have been carried out with chemo-prophylaxis against nosocomial infections at a children's hospital. 291 children of all ages were given a continuous small dose of sulfathiazole during the whole stay at the hospital. 309 children represented a control material which was not treated. The frequency of infection was considerably less in the treated group, and the difference is statistically significant.
3. When nosocomial infections occurred in the treated group in spite of the prophylaxis, they were found to be more moderate than the infections in the control group.
4. No toxic reactions of any importance were observed.
5. The risk factors at chemo-prophylaxis with compounds belonging to the sulfanilamide group are discussed. Finally, the practical applicability of the method is touched upon.

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FROM THE PEDIATRIC CLINIC OF KAROLINSKA INSTITUTET AT KRON-  
PRINSESSAN LOVISA'S CHILDREN'S HOSPITAL, STOCKHOLM.  
HEAD: PROFESSOR A. LICHTENSTEIN.

## **Treatment of Children's Diabetes.**

### **Ten Years' Experience without Dietetic Restrictions.**

By

**A. LICHTENSTEIN.**

A study of the history of diabetes diet shows that there are no definite scientific bases for a diet composed in a certain particular way. Especially in earlier times, but also later, the most diverse proposals regarding high protein and low protein, high fat and low fat, high carbohydrate and low carbohydrate diet have been submitted.

Thus, JOSLIN's collaborator, PRISCILLA WHITE, 1935, notes that we must take account of five different types of diet, namely high carbohydrate-low fat, low carbohydrate-high fat, moderate carbohydrate-moderate fat, low protein and high protein. In 1940 the same author states that »the qualitative prescriptions or ratios of carbohydrate, protein and fat depend upon the convictions of two schools of thought. If the student of diabetes believes that stimulation of the pancreas results in an alleviation of the disease or rest results in an alleviation, the diets high and low in carbohydrates are prescribed correspondingly.» The only common feature in the various diets recommended in the treatment of diabetes is the requirement that the conduct of life shall be regulated with strict regard to the diet.

If any valid scientific grounds for the superiority of a certain form of diet had existed, this diet would doubtless have soon superseded all the others. No such development has taken place. On the other hand, in the course of the score of years which have

elapsed since the introduction of insulin, the diet, which had previously been extremely restrictive, especially in regard to supply of carbohydrates, has in most places become more generous and, above all, richer in carbohydrates than before. In this way the diet prescribed for diabetics has gradually been brought into closer correspondence with that of healthy persons. Most diabetes therapists, however, have so far hesitated to take the decisive step of changing over to a quite normal dietary.

The first investigator who recorded experiences in the treatment of children's diabetes without any dietetic restrictions, was the German pediatricist STOLTE, of Breslau, 1931. In 1934 SÖDERLING, of Stockholm, reported certain good results obtained with this method of treatment.

In 1932 — without previous knowledge of STOLTE's work — the author himself proceeded, on a minor scale, to try the effect of free diet. Encouraged by the favourable outcome and afterwards by STOLTE's and SÖDERLING's experiences, I have since 1933 consistently carried out the treatment of diabetic children without dietetic restrictions. In the »Journal of Pediatrics» 1938, »Acta Pædiatrica» 1939, and various publications in the Swedish language, I have reported very satisfactory results obtained with this method. In the course of the last ten years it has been taken up in Finland (RÄIHÄ), Norway (SUNDAHL), Denmark (BOJLÉN), and Germany (FRICK and MUSTERLE, E. MÜLLER etc.), everywhere with success. As I now can look back upon more than ten years' experience with this treatment, I have considered it desirable to publish my material and my views on the treatment of diabetes in children, — especially as it has been stated (*e. g.*, by JOSLIN) that no report on the results of a ten years' experience with free diet had yet been issued.

It is not a mere coincidence that the treatment of diabetes without dietetic restrictions has been taken up by pediatricists. Diabetes in children is essentially different from diabetes in adults, and the difficulties incidental to a more or less rigorous diet which is to be observed not for weeks or months, but for life, make themselves much more strongly felt in children than in adults.

In children, diabetes is firstly almost always of a severe character: during the pre-insulin era, despite the strictest diet, it led to death within twelve months or at most two years. The diet was of little use, but made the children's last months a martyrdom.

Diabetes in children is moreover characterized by a more labile metabolism than diabetes in adults, with sudden oscillations between hyperglycemia and hypoglycemia and with a perpetual menace of ketosis. Children are also more liable to infection than adults, and the course of the disease is often complicated by infections of different kinds.

Furthermore, diabetic children owing to their growth and development, require an adequate supply of food, whereas adult diabetics need only by maintained in equilibrium and can even periodically be kept with advantage on a somewhat low diet.

Finally, psychological factors must be taken into account. The diabetic child should develop not only physically, but also mentally, in a normal way. We should therefore, as far as possible avoid placing these children in a position apart from other children, and thus prejudicial to their mental development, character formation and social adjustment. And the perpetual maintenance of a certain diet undoubtedly places them in such a position.

All the considerations above enumerated conduce to complicate the diabetic treatment of children, so that the results obtained tend to become worse than in the case of adults. We must therefore look for better methods of treatment. Especially for a doctor who is familiar with child psychology, the question then arises: *are dietetic restrictions really necessary for satisfactory treatment of the disease in children, or is it possible, with the aid of insulin, without special diet to keep the disease under control and promote a favourable physical and mental development?*

This question cannot be answered without a thorough and unprejudiced testing of a sufficiently large material for a sufficient length of time. Theoretical speculations, more or less influenced by the hidebound ideas of the pre-insulin period, are quite worthless. It is at once evident that, if equally good or even better results can be attained by a treatment without dietary restrictions, such

a treatment in any case as regards children, would be far preferable.

At my clinic this question has been subjected to thorough testing, for more than ten years. Similar material from the pediatric clinic at the Norrtull Children's Hospital in Stockholm, has been placed at my disposal by the courtesy of Professor Wallgren and conduces to support my own observations.

The material dealt with in the present study embraces the ten-year period 1934—1943; it consists of 169 cases of diabetic children and young persons up to the age of twenty-two. Table 1 shows the *age of manifestation* of the disease.

Table 1.

Age at time of onset	-1	-2	-3	-4	-5	-6	-7	-8	-9	-10	-11	-12	-13	-14
Number of cases .	2	8	15	13	9	14	17	11	16	14	14	13	12	11

These cases were observed during a period ranging from one to twenty years — on entirely normal diet up to twelve years. About half the number of children have been put on normal diet for five to ten years. This, of course, is not a lengthy period as regard a lifelong disease. It is nevertheless sufficiently long to enable one to survey certain results and see whither they are pointing, — though on certain points reservation must be made for what may happen in the sequel.

These cases were at first regularly examined at the clinic. The diagnosis was made on the basis of the ordinary urine and blood examinations and the glucose test. The material consisted throughout of severe cases of diabetes cases with a marked tendency to ketonemia, pre-coma and coma.

During the hospital treatment the cases are followed with *excretion diagrams*, on which the amount of urine sugar in samples, taken at 6, 9, 13, 16, 19 and 24 o'clock, as well as blood sugar, amount of urine, insulin dosages and possible acetonuria are recorded.

After discharge the patients are kept under control at our diabetic out-patient department or, if they live elsewhere, by

doctors, or at hospitals, in their places of residence. The controls are adapted to the nature of the case and are made from once a week till a few times a year.

Fresh cases receive from the outset »free diet». By this I mean a diet completely corresponding with that of healthy children. The diabetic children are allowed at first to take the ordinary hospital fare and eat their fill. In their homes they are then allowed to share the diet of their brothers and sisters and playmates and to satisfy their individual taste within the same limits as for healthy children. Even sugar and sweets in reasonable amounts are permissible. At the hospital the amounts of food which the children *spontaneously* consume are weighed and measured. In their homes no weighing or measuring of the food is required. The only restriction made is to avoid overindulgence, a rule which should apply in equal degree to all children, thus also to healthy ones.

Children who had previously kept a more or less strict diet are kept on the same diet for the first few days at the hospital and are then at once transferred to »free diet». In these cases, the reaction to the change is studied.

The change from diet to free fare is shown in Fig. 1.

The children receive the amount of insulin required to produce a good general condition, a feeling of well-being, a satisfactory increase in weight, a moderate amount of urine and complete freedom from acids in the urine. On the other hand, I attach less importance to a moderate rise in blood sugar and to a moderate or small excretion of sugar, in itself. Indeed, I prefer some excretion of sugar to complete freedom from sugar in the urine, as one then runs a smaller risk of hypoglycemia and ketosis, the two dangers which in the first place menace the diabetic child.

The transition between dietetic treatment and »free diet» could always be made without difficulty. In these cases ravenous carbohydrate hunger was often immediately found in children who had previously been kept on a strict carbohydrate restriction. Thus children who had previously received a diet of less than 100 gr carbohydrates per day, during the first few days of the »free diet» consumed 250—300 gr carbohydrate per day. Already

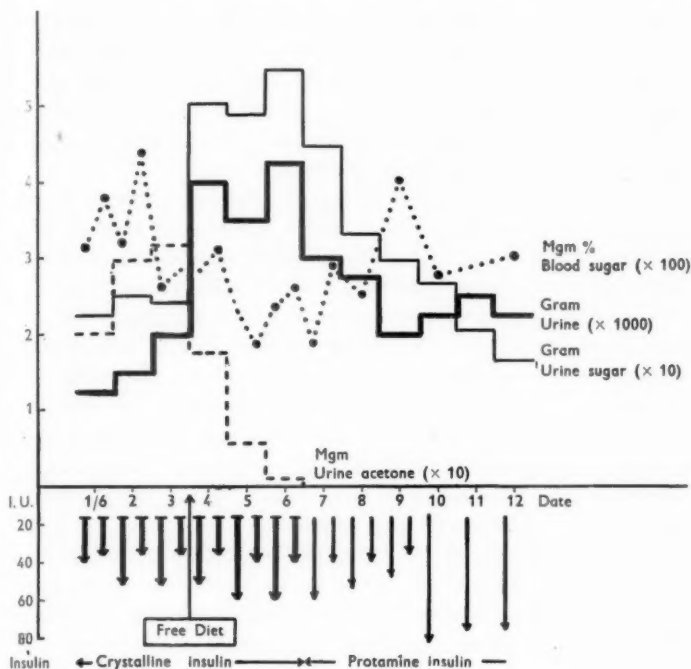


Fig. 1. Change from restricted diet to 'free diet'.

after a few days, however, they spontaneously adjusted themselves to a more moderate consumption of carbohydrates, which, however, was always considerably higher than the amount previously permitted. As a rule it was about of 150–250 gr per day, corresponding to 6–7 gr per kg body-weight and day with relatively small variations from day to day. The youngest children of 1–2 years consume considerably more, up to 8–10 gr or more per kg body-weight and day. Some older children also seem periodically to show a relatively large need of carbohydrates.

These children spontaneously consume as a rule 2–3 gr of protein and 2.5–3.5 of fat per kg and day.

The supply of calories was as a rule spontaneously maintained



at 80—100 for children under five, at 60—80 at the age of 5—10 years and 40—60 at the age of 10—15 years, all per kg body-weight.

The diet is thus a normal all-round fare, in which none of the ingredients are disproportionately increased at the expense of any of the others, as is the case with several of the proposed high-fat, high-protein or high-carbohydrate diets.

In judging the value of a certain diabetes therapy, a sufficiently long observed material must be thoroughly studied from different points of view. A child material must be examined with regard to the general condition, both physically and mentally, with regard to growth, increase in weight and puberal development. The carbohydrate metabolism must be studied with respect to the excretion of sugar, the blood sugar picture, ketonuria and the tendency to coma. The children's susceptibility to infection, their mode of reaction to acute infections and tuberculosis must be thoroughly examined. Complications, especially cardiovascular, must be carefully searched for, and finally the mortality must be studied for a sufficiently long period.

*The general condition*, as soon as the children have been well adjusted and free from infection, is throughout very satisfactory. The children show no increased hunger or thirst, no polyuria and in general no subjective symptoms whatever. The small children play like healthy children. The school children manage their school work well and, almost without exception, take part without difficulty in gymnastics and sports with their school fellows.

*From a psychological point of view*, the freedom from the compulsion to keep a diet, and thus the liberation from a regime which marked them out from healthy children proved to be very beneficial. The children have a feeling of well-being and joy of life. In my opinion, this has a positively favourable effect on their metabolism, which is by no means surprising, as it is well known that mental strains such as worry and tension have a very unfavourable effect on diabetes.

A study of the *growth in height* is of interest, seeing that children with a neglected or badly controlled diabetes, show a stunted growth, up to dwarfism. In my material the growth in

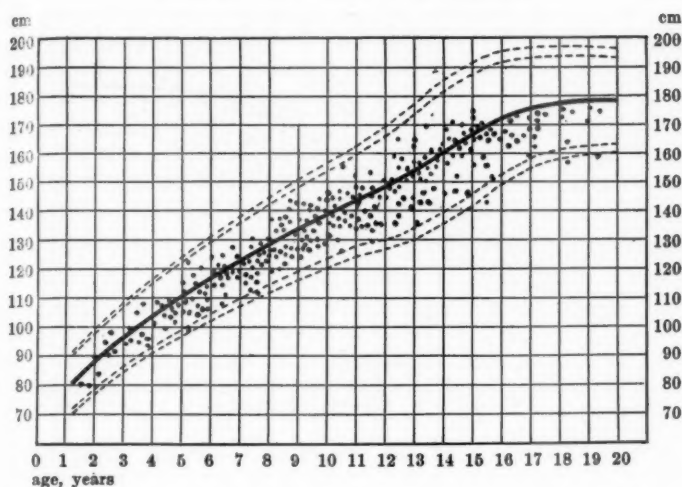


Fig. 2. Height in diabetic boys of different years of age. Whole line = means. The dotted lines delimit the spaces between  $2\frac{1}{2}\sigma$  and  $3\sigma$  on each side of the means. (After BROMAN, DAHLBERG & LICHTENSTEIN).

height was quite normal. The following Figs. 2 and 3 show for boys and girls respectively that the height at different ages, with a few isolated exceptions, keeps well within the normal limits of deviation for healthy children in Sweden (according to BROMAN, DAHLBERG and LICHTENSTEIN, 1940).

The normal growth in height indicates that the disease in this material was under good control. It is of interest to note that WHITE in a »Preliminary Statistical Summary of Diabetes in Juvenile Patients surviving fifteen or more years' duration of the disease», in 150 cases found pseudo-dwarfism in 20 per cent.

Also the *increase in weight*, as shown by Figs. 4 and 5 for boys and girls respectively, has kept well within normal limits. The body-weights at different ages show a normal deviation, as compared with BROMAN, DAHLBERG and LICHTENSTEIN's normal values.

As an argument against the free fare, the risk of over-feeding has been pointed out. In the present material this is not the case.

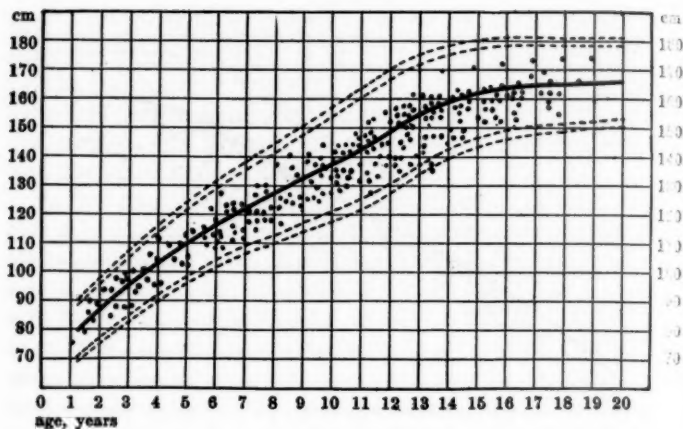


Fig. 3. Height in diabetic girls of different years of age. Whole line = means. The dotted lines delimit the spaces between  $2\frac{1}{2}\sigma$  and  $3\sigma$  on each side of the means. (After BROMAN, DAHLBERG & LICHTENSTEIN.)

In my experience, most diabetic children show no tendency to fatness. In some children, however, this is the case. In such instances, it is the obesity of the child, but not its diabetes, that requires dietetic restrictions, just as is the case with an obese non-diabetic child.

I desire also to emphasize that the insulin treatment naturally must not take the form of »insulin fattening», which, as a rule, can be avoided without difficulty.

One might *a priori* anticipate that the hormonal unrest during the *age of puberty* might unfavourably affect the disease and perhaps impede or completely prevent the carrying out of the »free diet» system during that period. Apprehensions to that effect have in fact been expressed by the opponents of »free diet». These apprehensions are not warranted. A large number of our diabetic patients during the period of observation have passed through their puberal development without retardation and without presenting any difficulties whatever in regard to control.

As regards the *carbohydrate metabolism*, I have as already mentioned, not attached much importance to freedom from sugar

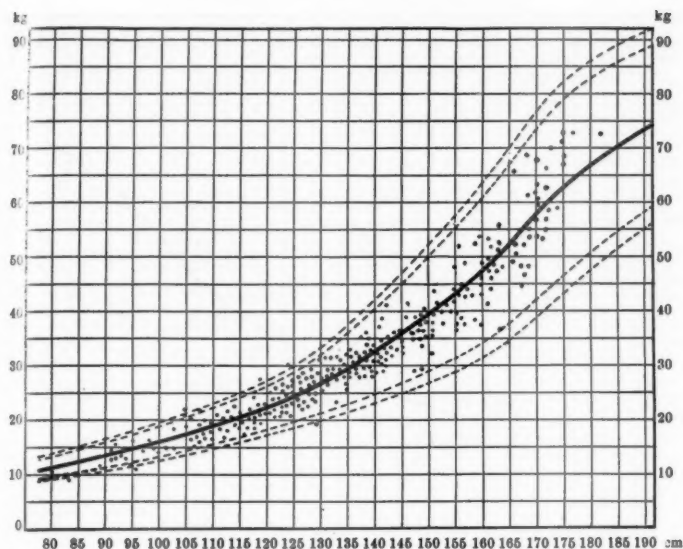


Fig. 4. Weight in diabetic boys of different heights. Whole line = means. The dotted lines delimit the spaces between  $2\frac{1}{2}\sigma$  and  $3\sigma$  on each side of the means. (After BROMAN, DAHLBERG & LICHTENSTEIN.)

in the urine. If the children have felt well, have not shown greater hunger or thirst, polyuria or itch, and if they have normally increased in weight, it does not worry me if the urine contained up to some tens of grams of sugar per 24 hours. As a rule, the degree of glycosuria was less than 10 per cent. of the carbohydrate intake. No undesirable consequences were observed. On the contrary, it is evident that in this way we run a much smaller risk of hypoglycemic states, which so often disturb the dietetic treatment, than if we aim at obtaining complete freedom from sugar in the urine. Severe hypoglycemic attacks were in fact very unusual in our material after we had consistently allowed a »free diet». Such attacks now occur only quite occasionally in cases of acute disease with a loss of appetite or vomiting, or if the children have been taken out of their normal course of life with regular meals, as, for example, during a long journey. Nor, — unlike several

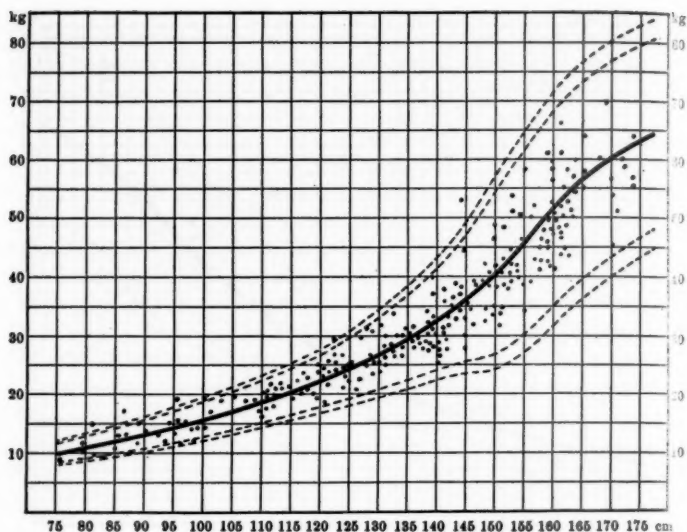


Fig. 5. Weight in diabetic girls of different heights. Whole line = means. The dotted lines delimit the spaces between  $2\frac{1}{2}\sigma$  and  $3\sigma$  on each side of the means. (After BROMAN, DAHLBERG & LICHTENSTEIN.)

previously published investigations —, did my material show any case of death from hypoglycemic shock. The excretion of urine-sugar, relatively to the generous supply of carbohydrates, was moderate and not seldom remarkably low.

Not insisting on freedom from sugar in the urine, I did not aim at »normalization» of the blood sugar picture. One might *a priori* expect that the blood sugar, in view of the far larger supply of carbohydrates, would be much higher than in dietetic treatment, unless the insulin dosages were considerably increased. This was not found to be the case. In some of the cases, where diet had been superseded by »free fare», the insulin dosage had to be somewhat increased, whilst in others it had actually been somewhat reduced, despite a considerably larger supply of carbohydrates. The blood sugar fasting values in well controlled cases usually range between 100 and 200 mg %. The curve for the 24

hours often shows considerable variations. Occasionally it is somewhat higher, but not seldom lower as well as more regular, than before the change-over to »free diet».

No drawback from the non-normalization of the blood sugar was ever observed. The supposition of a connection between high blood sugar and the appearance of cardiovascular lesions has not been confirmed, as is also stated by WHITE.

If I have thus permitted a small or moderate excretion of sugar, no ketonuria was tolerated and the fulfilment of this requirement, which I consider to be decisive for a favourable course, was found to be greatly facilitated by the »free diet». After transition to that regime one frequently observes the disappearance of a previously marked tendency to ketonuria. Children who before had shown constant symptoms of ketonuria and in many cases had to be hospitalized again and again because of menacing or developed coma, could be treated for years, after the removal of all dietetic restrictions, without showing a trace of ketonuria.

In point of fact the frequency of pre-coma and coma was reduced by the »free diet» in an extremely high degree, as compared with previous experience.

This is closely connected with our experiences regarding the *reaction of our patients to acute infections*. Such infections, influenza, angina, measles, etc., often set their mark on the course of the disease of diabetic children, bring them out of metabolism equilibrium and lead to ketonemia and coma or in other cases to an opposite danger — gastric retention and hypoglycemia.

One of the principal criteria of a good dietetic treatment is therefore the way in which intercurrent acute infections affect the condition. We see now how on free diet such infections are overcome much easier than before and lead to far less serious disturbances in the metabolism of the diabetic children. This was particularly striking in a number of cases which had previously been put for years on a rationed diet and which, owing to apparently insignificant infections, had often developed pre-coma and coma. In this respect the »free diet» entailed a striking change for the better. In this connection the reader may be reminded of the old experience from the pre-insulin era that diabetic children

in cases of intercurrent infections were placed with advantage on free diet with a generous supply of carbohydrates, a method which doubtless is also applied by many of those who otherwise still insist on the necessity of strictly rationing the diabetic diet.

Opponents of »free diet» have expressed apprehensions that it might enhance the *risk of tuberculosis*. In my material there is one death from miliary tuberculosis, a few months after the onset of the diabetes. But otherwise we have found that 41 children sooner or later showed a positive tuberculin reaction and were afterwards continuously controlled clinically and roentgenologically, in most cases for 5—10 years after the tuberculin reaction had become positive, without an active tuberculosis having occurred in a single one of these cases. Merely in one case quite a slight lung focus, which rapidly healed, was observed. Some of our tuberculinpositive diabetic children had also had measles or whooping cough without any activation of their tuberculosis. It was thus found that our patients overcame tubercular infection quite as well as non-diabetic children.

*Diabetic complications* occurred in a remarkably small degree.

We have taken particular care to look out for *cardiovascular complications*, also by blood pressure and roentgen examinations as well as blood cholesterin determinations. No rises in the blood pressure were observed, nor any roentgenologically demonstrable calcifications of the blood vessels. In one case in the year 1944 — which is not included in this survey —, of a 25-year-old woman who had suffered from diabetes for twenty years and who for several years had had a complicating chronic pyelonephritis, arteriosclerosis was observed in the vessels of the legs.

As regards the plasma-cholesterol, KARLSTRÖM found in my material on an average somewhat higher values than in a control material, but almost throughout normal values — as a rule below 230 mg. No relation between cholesterol and blood sugar or urine acetone could be ascertained.

Thus in my material the risk of juvenile arteriosclerosis in well-controlled diabetic treatment without dietetic restrictions could not be confirmed, contrary to what *e. g.* JOSLIN had found in uncontrolled cases. Among the above-mentioned 150 cases of



a least 15 years' duration under treatment with diet and insulin, WHITE found arteriosclerosis in no less than 1 to 6 during the second and 1 to 5 in the third decade. As compared with this, the results in my material seem to be far better so far as the risk of sclerosis is concerned.

In one case a slight unilateral *cataract* was observed. Among WHITE's already mentioned 150 cases seven patients had cataract.

In a number of cases a slight, but transient *enlargement of the liver* was observed partly by palpation, partly by roentgen examination, almost always at the beginning of the disease. In two or three cases the enlargement of the liver has been more marked, but in these cases too proved to be transient.

Otherwise no complication whatever had occurred.

The *mortality* in my material during the ten-year's period 1934—1943 was remarkably low. Out of 169 patients only eight died. One child was murdered by the father. One died of miliary tuberculosis with meningitis a few months after the onset of the diabetes. Another child died of pleural empyema with a diffuse purulent peritonitis and one of scarlet fever. One patient died at the age of 24 of sepsis after a phlegmon in the mouth. Only three died from coma. One of them died at a hospital in the provinces and had received insufficient insulin doses, two died at the clinic, one of them of anuria when the diabetic coma had cleared. The total mortality (including the murdered child) amounts for the ten-year's period to 4.7 %.

A comparison between my material and previously published data regarding the mortality of insulin-treated children's diabetes is greatly complicated by the fact that in regard to them no statistical compilation has been made in which the period of observation is taken into account. So far as I know, no dietetic material fully comparable with mine exists. The nearest comparable material seems to be that of SELANDER from Gothenburg. In this material 27 deaths out of 155 patients, or 17.4 %, are reported for the fifteen-year's period 1925—1939 and for the five-year's period 1935—1939 8 deaths out of 137 or 5.8 %. JOSLIN reports for the fifteen-year's period 1922—1937 a mortality of 9.7 % (1 063 cases with 104 deaths). Among WHITE's above-



mentioned 150 cases, which were followed for at least fifteen years, there were 12 deaths, or 8 %.

Summing up, the results of a more than ten years' treatment of children's diabetes without dietetic restrictions are very satisfactory: a good physical and mental development, a minimum of coma, hypoglycemia or other complications and a lower mortality than has hitherto been obtained with dietetic treatment. The essential conditions for satisfactory results are firstly a good insulin treatment from the outset and secondly a careful continuous control.

As regards *insulin treatment*, the first consideration is the choice of a preparation. Previously, treatment without dietetic restrictions required two and often even three doses of ordinary insulin per day. Now that we have obtained new insulin preparations with a slow resorption the treatment has been simplified. I have used with great advantage *Hagedorn's protamininsulin* (Insulin Retard) and have thus been able in most cases to reduce the number of injections to one per day. As a rule it is given in the morning, about half an hour before the first meal. In a minor number of cases an evening dose is also required. No account has been taken of the endogenous liver rhythm, nor was there any necessity for this in my material.

*Zinc protamin insulin* in most cases was found to be less beneficial for the children, who with this insulin more frequently showed a tendency to hypoglycemia than with the protamin insulin without zinc. Occasionally, however, one finds a child who adjusts itself more easily to the insulin with zinc than without it. In a single case the old type of insulin was found to be superior to the protamin type, to which the child could not adjust itself, whereas such adjustment was easy with ordinary insulin.

The need of insulin varies greatly from case to case and must be individually tested for each child. To adjust the insulin dosage according to the supply of carbohydrates is not practicable, at any rate as regards children. In some cases quite small doses are required at first and afterwards gradually increasing amounts, and in the nature of things diabetic children during growth generally require an increasing amount of insulin. In other cases, where

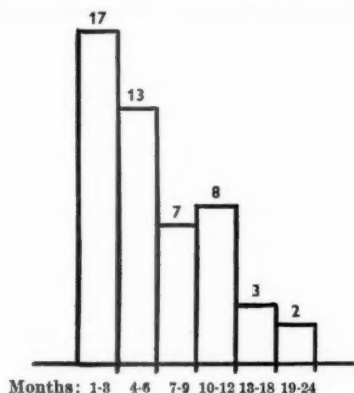


Fig. 6. The length of the initial phase.

the onset is more acute, large doses are required at first, but they can afterwards be reduced, often in a very considerable degree. In some cases, periods with large requirements of insulin alternate with periods in which a far smaller amount of insulin is found to be sufficient. Not infrequently a somewhat reduced need is observed in the summer, which is perhaps connected with seasonal variations in the insulin output of the body itself.

Thus, especially in the initial stage of the disease, very careful control and flexibly adjusted changes in the insulin supply are required. This phase, during which the need of insulin is extremely labile, varies considerably in length. ROTHE MEYER, on the basis of my material, studied *the duration of the initial phase* in fresh cases of diabetes treated from the outset with free diet and with protamin insulin or — in a minor number of cases — with zinc protamin insulin. He studied how long it had taken before the insulin dosage has adjusted itself to a uniform level with a duration of at least six months without greater variation in the amount of insulin than 4 units from the mean level. He found that one-third of the cases had been thus stabilized within 2 months, two-thirds within 6 months and 90 % within one year after the commencement of the treatment (see Fig. 6).

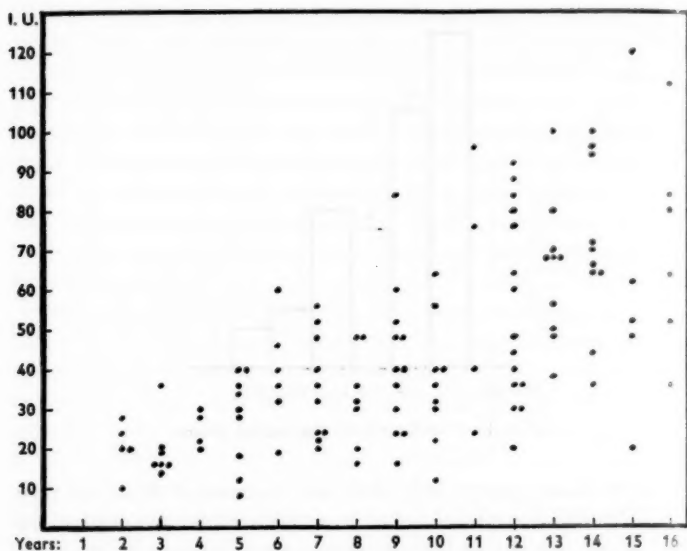


Fig. 7. Insulin dose during the 2nd year of the free diet.

If one desires to give an idea of the need of insulin in treating children's diabetes without dietetic restrictions, it is desirable to examine the insulin doses *e. g.* during the second year of the free diet, when practically all cases have attained a certain stability with respect to the need of insulin. The following Figure (7) shows firstly a certain relation between the patient's age and the insulin requirement, secondly that the doses vary between 10 and 120 international units per day (average about 40 units).

The following Figure (8) shows the *maximum insulin doses* required in my cases at any time during the observation period (apart from the attacks of coma). The variation here too is between 10 and 120 units, but the average is naturally higher (about 60 units).

As stated, it is necessary, in order to obtain good results, to exercise a *careful continuous control*, with at first frequent and gradually more occasional examinations. In the case of children,

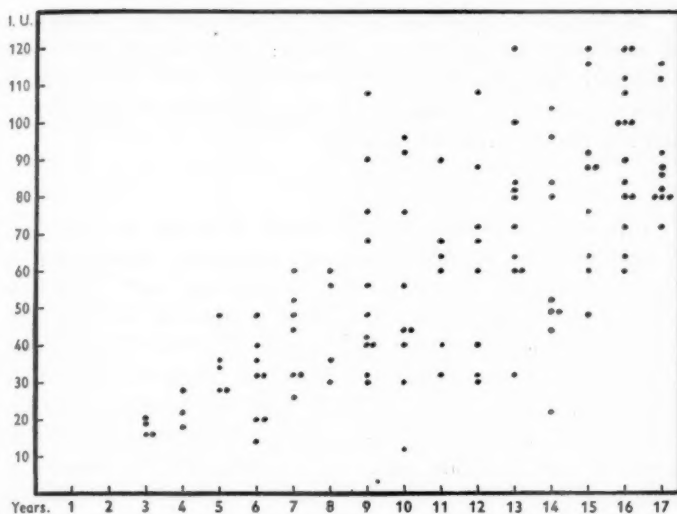


Fig. 8. Maximum insulin dose with free diet.

the control involves *good cooperation with the homes*, especially with the mothers. It is therefore necessary to give instructions to the mothers. They must learn the principal features in the clinical treatment of the disease, they must learn to recognize, in particular, such changes in the child's condition as require a modification of the insulin dosage, and they must learn to use the insulin syringe correctly. Many mothers in our Swedish clientele can be taught to make qualitative and sometimes also quantitative sugar tests and even to perform Gerhard's and Legal's test of ketone bodies in the urine. A more important matter, however, is to draw their attention to the significance of *greater thirst* and *large amounts of urine* as indications of unsatisfactory adjustment, and to the importance of immediately getting into touch in such cases with the doctor treating the case. Another important matter is to get the mothers to understand the *signs of hypoglycemia* and how it is counteracted. The importance of a *regular conduct of life* with regular meals should also be strongly emphasized.

As regards the *injection technique*, it is particularly important to emphasize the necessity — besides strict asepticism —, of constantly *changing the place of injection*. This instruction is often neglected, the consequences being large lipomatous infiltrates and bad resorption of the insulin.

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Clinical experience evidently argues in favour of free diet. It may be asked whether any cogent theoretical reasons can be adduced against it. In my opinion this is not the case. Our knowledge of the etiology and pathogenesis of diabetes are still very imperfect. We know that the regulation of the carbohydrate metabolism is a very complex function, in which, in addition to the insulin system, the sympathetic nervous system and the internal-secretion glands — the hypophysis, the thyroid and the adrenalin system — take part. We know also that, by changes in diet in various ways, we can markedly affect the metabolism equilibrium, and in a particularly high degree in children who show more labile equilibrium between the internal secretion organs than adults.

On the other hand, we cannot fully judge the effects of our dietetic measures in this regard. Nay, as regards the pancreas in diabetes we do not even know whether a generous or scanty supply of carbohydrates is an advantage. In this connection it is interesting to note BEST's experiments on rats, which showed that »normal diets result in the highest insulin content of the pancreas, low carbohydrate-high fat the lowest, and high carbohydrate between the two». Though we are not entitled to regard these experiments as directly applicable to diabetes in man, they by no means argue against normal diet for these sufferers.

Nor do the objections to a more generous supply of carbohydrates and to a bolder view of the blood sugar and the excretion of sugar in diabetics hold good. As far back as 1914 ALLEN and DUBOIS showed calorimetrically that a diabetic utilized the carbohydrates despite of hyperglycemia and glycosuria, and this result was afterwards confirmed, for example, by BRIDGE and WINTER from the John Hopkins hospital in 1939. It is the utilization and

not the excretion of the carbohydrates that is of importance, as in benign glycosuria. TOLSTOY and associates in recent years treated diabetics with good results, without aiming at freedom from sugar in the urine.

Proceeding from STAUB's investigations, BRENTANO likewise regards the heightened blood sugar picture as a compensatory phenomenon, useful for the diabetic. And it should be born in mind that, as BRENTANO puts it, carbohydrates are the fuel of life even for diabetic.

Therefore, in my opinion, it may quite theoretically be questioned whether our present knowledge of diabetes even entitles us to give definite dietetic instructions, especially if they involve a reduced supply of carbohydrates in cases of this disease. At any rate as regards children, such interventions may entail consequences which as yet cannot be fully judged. In any case no theoretic reasons can fairly be adduced against the »free diet» for diabetic children. For the present, an unprejudiced clinical testing must pronounce the verdict.

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For about 35 years I have been in a position to treat and follow the destinies of diabetic children. The first 15 years of this period fell within the pre-insulin era, with its hopeless prognosis. In the course of the following 20 years, I at first treated diabetic children, like most other doctors, with a strict, low-carbohydrate diet plus insulin. I gradually changed over to a diet richer in carbohydrates but still limited, and finally I have now for more than 10 years adopted an entirely »free diet». I can thus judge this »free fare» against the background of a long experience in regard to different methods of treating children's diabetes and their value. Without hesitation, I now consider myself justified in stating that *diabetic children, as a general rule, should be treated without any dietetic restrictions whatsoever.*

### Summary.

Experiences during the 10 years' period 1934—1943 in regard to 169 cases of children's diabetes without any dietetic restrictions whatever were very favourable. The children showed a good physical and mental development and a minimum of coma, hypoglycemia or other complications. The total mortality was merely 4.7 %.

Protamin insulin in doses of 10—120 units per day entailed less tendency to hypoglycemia than zinc protamin insulin. As a rule one injection per day was found sufficient.

Stress is laid on the necessity of close cooperation with the homes, if good results are to be obtained.

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## Über den Einfluss der Narkose auf den intrakraniellen Druck.

Von

GUSTAF LINDBERG.

Bei der Lumbalpunktion im Kindesalter ist es nicht selten schwierig ohne allgemeine Narkose auszukommen. Besonders im Spielalter ist es oft unmöglich das Kind so zu beruhigen, dass es während der Druckmessung die Muskeln genügend entspannt, und besonders in den Fällen, wo an die Punktion eine intralumbale Injektion von Serum oder anderen Arzneimitteln angeschlossen werden soll und die Punktion dadurch etwas länger dauert, greift man gern zur allgemeinen Narkose umsomehr als diese in diesem Alter ganz gefahrlos ist. Auch beim Säugling und beim älteren Kinde ist die Narkose in den Fällen wertvoll, wo man eine intrakranielle Blutung nicht ausschliessen kann und die Verletzung der Venen des Lumbalkanales vermeiden will. Es ist auch vorgeschlagen worden, die Narkose in den Fällen zu verwenden, in denen man den Druck besonders genau feststellen will und das Pressen und Würgen eines unruhigen Kindes vermeiden will. Es erhebt sich aber dann die Frage, ob das Narkosemittel und die Narkose an sich für die intrakraniellen Druckverhältnisse ohne Bedeutung sind, und ob man somit die während der Narkose ermittelten Druckwerte ohne Weiteres als zuverlässig betrachten kann.

In der pädiatrischen Literatur finden sich keine diesbezüglichen Angaben und dasselbe negative Ergebnis gibt eine Durchsicht der mir zugängigen internen und chirurgischen Literatur. Die Variationen des intrakraniellen Druckes unter verschiedenen physiologischen und pathologischen Bedingungen sind Gegenstand



zahlreicher experimenteller Untersuchungen beim Tier gewesen; aus denselben ist aber nichts hervorgegangen, was für die Klinik von Interesse war. Der erste, der Beobachtungen über die intrakraniellen Druckverhältnisse anstellte, dürfte Mosso gewesen sein, der im Sinus longitudinalis einen etwas höheren Druck als in anderen Venen feststellen konnte.

Über den Einfluss von Narkosemitteln auf den intrazerebralen Druck im Tierversuch liegen nur wenige Versuche vor. ROY und SHERRINGTON glaubten beim Hunde feststellen zu können, dass Chloroformnarkose durch Verminderung des allgemeinen arteriellen Druckes eine Verminderung des Gehirnvolumens hervorruft. Intravenöse Injektion von Äther in therapeutischen Mengen rief eine starke Erweiterung des Gehirns hervor, die wahrscheinlich durch eine Steigerung des venösen Blutdruckes bedingt war. Inhalation von Äther rief zuerst eine Kontraktion dann eine Erweiterung des Gehirns hervor. BAYLISS und HILL untersuchten die Druckverhältnisse im Sinus longitudinalis unter verschiedenen Bedingungen, unter anderem auch in der Narkose. Sie fanden, dass sowohl Chloroform als auch Äther eine Verminderung des Venendruckes hervorrufen, welche Drucksenkung sie durch eine Verminderung des allgemeinen arteriellen Blutdruckes in der Narkose erklären. PICK untersuchte die Strömungsgeschwindigkeit des Blutes im Gehirn in der Weise, dass er die aus der Vena jugularis abfließende Blutmenge unter verschiedenen Bedingungen feststellte. Seine Versuche ergaben, dass man bei Chloroform und Äthernarkose wahrscheinlich mit einer Hyperämie des Gehirns zu rechnen hat. WINKLER fand, dass die Chloroformnarkose beim Tier eine Vermehrung des Gehirnvolumens hervorruft. DIXON und HALLBURTON fanden, dass das Chloroform eine bedeutende Steigerung des zerebrospinalen Druckes hervorruft. Äther bewirkte bei Inhalation nur eine geringe Steigerung. Die Messungen wurden in der Weise ausgeführt, dass ein Manometer direkt in die Schädelkapsel eingefügt wurde. Diese Versuche sind demnach sehr wenig erläuternd. Eine Messung des zerebrospinalen Druckes unter Bedingungen, die denen, welche unter klinischen Verhältnissen vorkommen, ähnlich sind, d. h. durch Beobachtung der Druckschwankungen bei Lumbalpunktion

während der Narkose, wurde bisher nicht vorgenommen, wenigstens ist in der Literatur keine Mitteilung über solche Versuche zu finden. Die Ergebnisse der Tierversuche sind, wie aus der oben gegebenen Zusammenfassung hervorgeht, sehr widersprechend und scheinen für die Klinik ohne Wert zu sein.

Nun hatte ich seit mehreren Jahren nicht selten Gelegenheit gehabt festzustellen, dass die Messung des Druckes der Lumbalflüssigkeit bei Lumbalpunktion in Narkose keine zuverlässigen Werte ergab, und besonders hatte ich beobachtet, dass in Fällen, wo ich infolge Schädeltraumen eine bedeutende Erhöhung des Lumbaldruckes fand, der Druck nach Genesung des Kindes dieselben hohen Werte aufwies als zur Zeit der anfänglichen Schädelerschütterung. In diesen Fällen wurde die Druckmessung in der Narkose deshalb vorgenommen, weil ich die nicht seltene Blutbeimengung zum Liquor durch Verletzung der Venenplexus im Lumbalkanal tunlichst vermeiden wollte. Diese kommt im Kindesalter recht oft bei unruhigen Kindern zustande und kann in Fällen, wo man eine traumatische Ursache der zerebralen Symptome in der Anamnese findet, leicht zu fehlerhaften Schlüssen Veranlassung geben.

Über das Verhalten des intrakraniellen Druckes während zu therapeutischen Zwecken vorgenommenen Barbiturnarkosen bei Psychosen liegen jedoch zwei Untersuchungen vor. BUTLER fand, dass die intravenöse Injektion von 0,5 g Evipan-Natrium eine abrupte Senkung des Lumbaldruckes um 50 mm Wasser hervorruft. Diese Senkung fand schon während der Injektion statt. BUTLER ist der Ansicht, dass die Ursache der Senkung eine Verminderung des zerebrospinalen Kapillarendruckes und des Volumens der Hirngefäße ist. HORSLEY, der 100 Fälle beobachtete, fand dieselbe Senkung bei Verwendung von Nembutal, Evipan und Pentotal intravenös. Sie tritt nur bei Vollnarkose ein.

Da der intrakranielle Druck durch jede Steigerung des intraabdominellen Druckes, durch Pressen oder Würgen sehr schnell und effektiv in die Höhe getrieben wird, ist es selbstverständlich, dass das Exzitationsstadium der Inhalationsnarkose von einer Steigerung des intrakraniellen Druckes begleitet ist. Die älteste Beobachtung in dieser Hinsicht dürfte die von CARLE und MUSSO

sein, welche einen Mann mit einem Defekt im knöchernen Schädel während der Chloroformnarkose beobachteten. Sie fanden, dass im Exzitationsstadium eine Hyperämie des Gehirns eintrat, welcher im Stadium der Vollnarkose eine Anämie mit Einsenkung des Defekts folgte. Auch für das Avertin liegen Untersuchungen vor, namentlich von GARDNER und LAMB, welche den Einfluss der Avertinnarkose auf den intrakraniellen Druck, bei Applikation von 100 mg Avertin pro kg Körpergewicht rektal, untersuchten. Sie fanden, dass die Narkose von einer Steigerung des intrakraniellen Druckes um etwa 100 mm Wasser begleitet ist. Diese Untersuchung steht somit in Widerspruch zu den oben genannten von Horsley und Butler, die jedoch mit anderen Präparaten arbeiteten.

Die Drucksteigerung, welche im Exzitationsstadium der Narkose eintritt, beruht offenbar auf der intrazerebralen Venenstauung, die durch jede Muskelspannung im thorakoabdominalen Gebiet hervorgerufen wird. So schreibt ANTONI: »Dass man aus der Druckmessung bei unruhigen Patienten oder während der Narkose (sofern diese nicht tief ist) keine Schlüsse ziehen kann, weiss jedermann, der sich mit diesen Dingen beschäftigt hat.« Dies dürfte auch die allgemeine Meinung wiedergeben. Wenn jede Muskelspannung beseitigt ist, z. B. während der tiefen Narkose, ist die Messung des intrakraniellen Druckes durch Lumbalpunktion zuverlässig.

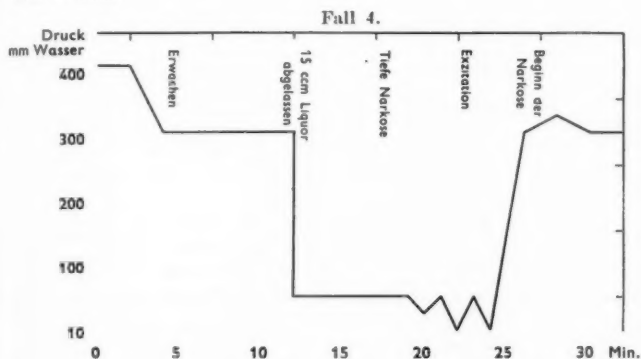
Jedoch liegen die Verhältnisse trotzdem in Wirklichkeit gar nicht so einfach, wie die von mir während nunmehr 20 Jahren gesammelten Beobachtungen lehren. Über diese will ich hier kurz berichten an Hand von einigen typischen Fällen, welche geeignet sind, auf den Einfluss besonders der Äthernarkose auf den intrakraniellen Druck während der verschiedenen Stadien der Narkose ein Licht zu werfen. Die ersten Fälle wurden von mir schon im Jahre 1925 beobachtet, die übrigen sind solche aus den späteren Jahren, die mir besonders geeignet scheinen, auf die vorliegende Frage ein Licht zu werfen. Die Untersuchung wurde, seit meine Aufmerksamkeit darauf gerichtet worden war, dass auch in der tiefen Narkose abnorme Druckverhältnisse in den zerebrospinalen Räumen herrschten, so vorgenommen, dass der

Lumbaldruck in geeigneten Fällen womöglich zusammenhängend sowohl vor als auch während den verschiedenen Stadien der Narkose und auch beim Erwachen aus derselben bestimmt wurde.

*Fall 1.* V. G., 5 Jahre. Mit der Diagnose Meningitis tuberculosa aufgenommen. Lumbalpunktion in Äthernarkose. Druck in tiefer Narkose 270 mm Wasser. Liquor normal. In wenigen Tagen symptomfrei. Eine Woche nach der Aufnahme erneute Lpt. Druck in tiefer Äthernarkose 240 mm. Die Narkose wird sofort beendet, wobei der Druck in 4 Min. auf 80 mm sinkt, indem der Pat. erwacht.

*Fall 2.* R. H., 4 Jahre. Wegen Krampfanfällen unklarer Genese aufgenommen. Lpt. ohne Narkose. Druck 40 mm. Nach Einleitung von Äthernarkose steigt der Druck sofort auf 270 mm, welches Niveau konstant bleibt. Die Narkose wird abgebrochen. Der Druck sinkt in 5 Min. auf 110 mm, nach 7 Min. auf 75 und nach 8 Min. auf 40 mm.

*Fall 3.* I. B., 1 Jahr. Krampfanfälle ohne Meningitissymptome und von unklarer Ätiologie. Lpt. ohne Narkose 150 mm. Wegen starker Unruhe des Kindes wird Äthernarkose eingeleitet, wobei aber der Druck mit Eintritt der tiefen Narkose auf 300 mm steigt. Dieser Druck bleibt konstant während der tiefen Narkose, und sinkt beim Erwachen schnell auf 70 mm.



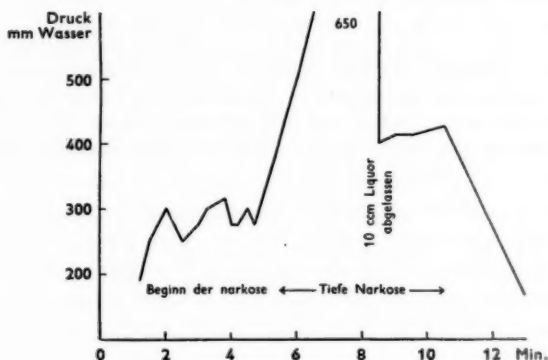
*Fall 4.* B. B., 2 Jahre. Pat. war von geringer Höhe auf den Kopf gefallen und wurde danach allmählich schlaff und teilnahelos. Bei der Aufnahme keine Meningitissymptome, Pat. ist aber nicht bei vollem Bewusstsein. Lumbalpunktion ohne Narkose. Präformierter Druck bei mässiger Unruhe 150 mm. Äthernarkose eingeleitet. Der Druck steigt schnell im Exzitationsstadium auf 400 mm, und steht, als die Narkose tief wird, ohne Veränderung auf dieser Höhe. 15 cem Liquor werden abgelassen, wobei der Druck auf 150 mm heruntergeht. Dieses Niveau

bleibt während der Narkose konstant. Als die Narkose abgebrochen wird, sinkt der Druck auf 50 mm. Der Liquor war normal und das Kind wurde nach einer Woche gesund entlassen.

*Fall 5.* S. L., 9 Jahre. Das Kind wurde wegen Kopfschmerzen und Erbrechen, welche Symptome als meningitisverdächtig erschienen, aufgenommen. Lumbalpunktion in Äthernarkose. Druck in tiefer Narkose 400 mm. Als die Narkose beendet wird, sinkt der Druck schnell auf 70 mm. Liquor normal.

*Fall 6.* K. L., 7 Jahre. Meningitis tbc. Lpt. in Äthernarkose. Druck 500 mm. 20 cem Liquor abgelassen. Druck 350 mm, allmählich auf 275 mm fallend. Bei Beendigung der Narkose sinkt der Druck auf 120 mm.

Fall 7.

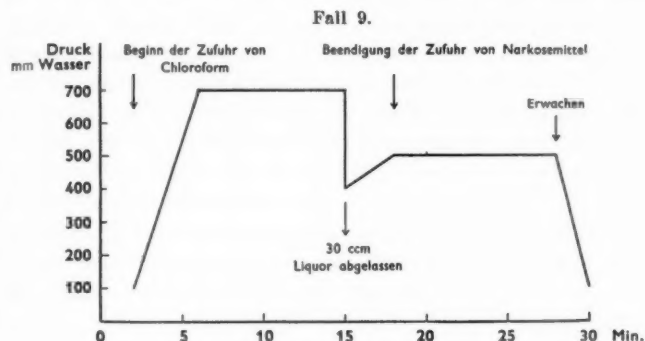


*Fall 7.* A. K., 7 Jahre. Meningitis tbc. Lpt. Druck vor der Narkose 180 mm. Äthernarkose eingeleitet. Der Druck steigt im Exzitationsstadium unregelmässig auf 250—310 mm. Beim Eintritt von tiefer Narkose und vollständiger Muskeler schlaffung mit ruhiger Atmung steigt der Druck schnell auf 650 mm. 10 cem Liquor werden abgelassen, wobei der Druck etwas sinkt um bald wieder auf 430 mm zu steigen. Als die Narkose beendet wird, sinkt der Druck mit dem Erwachen des Kindes auf 170 mm.

*Fall 8.* K. L., 5 Jahre. Wegen Kopfschmerzen unklarer Art aufgenommen. Keine Meningitissymptome. Äthernarkose. Lpt. in tiefer Narkose. Druck 450 mm, nach einigen Minuten auf 475 mm steigend. Beim Erwachen aus der Narkose sinkt der Druck allmählich auf 100 mm. Liquor normal.

*Fall 9.* A. B., Wegen Erbrechen vermeintlich zerebraler Art aufgenommen. Typische tuberkulöse Meningitis. Lpt. vor der Narkose

Druck 100 mm. Chloroformnarkose. Nach einigen Minuten ist der Druck mit dem Eintritt tiefer Narkose schnell auf 700 mm gestiegen. Der höchste Druck tritt deutlich in dem Moment des Eintritts des tiefen Narkose ein. 30 ccm Liquor abgelassen. Druck 400—500 mm. Nach Absetzen der Chloroformzufuhr dauert die tiefe Narkose noch 12 Min. Während dieser Zeit bleibt der Druck unverändert auf 500 mm. Gleichzeitig mit dem Erwachen tritt schneller Druckabfall auf 110 mm ein.



Fall 10. A. B., 3 Jahre. Imbezilles Kind. Wegen Krampfanfällen unklarer Art aufgenommen. Äthernarkose. Lpt. in tiefer Narkose. Druck 350 mm. Dieser Druck bleibt konstant. Nach Aussetzen der Narkose schläft das Kind ruhig 15 Min. weiter. Der Druck ist während dieser Zeit unverändert 350 mm. Erst bei Erwachen des Kindes sinkt der Druck schnell auf 100 mm.

Die Fälle, über die ich nun berichtet habe, zeigen, dass die Äthernarkose eine sehr starke Steigerung des durch Lpt. gemessenen intrakraniellen Druckes hervorruft. Diese Drucksteigerung tritt sofort bei Einleitung der Narkose ein, gleichzeitig mit der immer auftretenden Unruhe und Muskelspannung. Wenn die Exzitation beendet ist und ruhiger Schlaf eintritt, sinkt der Druck aber nicht, sondern bleibt gleich hoch oder noch höher als vorher. Es tritt die bemerkenswerte Erscheinung auf, dass die vollständige Muskeler schlaffung und Ruhe des tief schlafenden, ruhig atmenden Patienten mit einer hochgradigen intrakraniellen Drucksteigerung einhergeht, welche während der ganzen Dauer der Narkose fortbesteht. Bei Beendigung der Narkose und Er-

wachen des Pat. sinkt der Druck schnell wieder auf normale Werte. Diese Drucksteigerung ist von der im Exzitationsstadium der Narkose auftretenden Steigerung wie es scheint grundverschieden.

Die Ursachen der initialen Drucksteigerung liegen auf der Hand, wie schon oben bemerkt; der Mechanismus der in tiefer Narkose einsetzenden Drucksteigerung aber ist gänzlich unklar, wie auch das Vorliegen derselben unbeachtet geblieben ist. Veränderungen des intrakraniellen Druckes können in zweierlei Weise entstehen. Die eine Ursache sind Veränderungen der Menge des Liquors, die andere die Blutfüllung der Hirngefäße, vor allem der Venen. Die Zerebrospinalflüssigkeit wird von den Plexus choriodei abgesondert, wahrscheinlich durch eine Art Filtration, welche von der Blutfüllung derselben abhängig ist. Die Resorption der Flüssigkeit geschieht hauptsächlich durch die arachnoidalen Villi die im Verlauf der Sinus venosi lokalisiert sind. Über die Schnelligkeit der Zirkulation des Liquors wissen wir nicht viel, es spricht jedoch manches dafür, dass dieselbe ziemlich schnell vonstatten geht. Es scheint jedoch unmöglich, die Drucksteigerung in der tiefen Narkose durch Veränderungen der Menge oder des Abflusses des Liquors zu erklären, denn die Variationen des Druckes verlaufen so schnell in beiden Richtungen, dass sie nicht durch Veränderungen des Liquors erklärt werden können. In wenigen Minuten steigt der Druck um mehrere hundert Prozent und fällt beim Erwachen aus der Narkose ebenso schnell auf das vormalige Niveau. Entsprechend grosse und so schnell ablaufende Veränderungen der Liquormenge scheinen unwahrscheinlich. Die Ursache der Drucksteigerung muss deshalb eine andere sein. Der intrakranielle Druck wird durch alle Faktoren, die den venösen Druck innerhalb des Schädelkapsels erhöhen, sehr stark und schnell beeinflusst. Diese Veränderungen verlaufen so schnell, dass sie in Betracht gezogen werden müssen. Der Abfluss des venösen Blutes aus dem Schädelinnern wird von jeder Veränderung des intraabdominalen Druckes durch Pressen oder durch Muskelspannung verschiedenster Art oder durch Veränderungen des intrathorakalen Druckes durch Respirationsbewegungen bei geschlossener Rima glottidis hochgradig beeinflusst.



Die so hervorgerufene venöse Stauung ruft unmittelbar eine starke Steigerung des Lumbaldruckes hervor, welche den Druck fast unmittelbar verdoppeln kann. Der Druck kann ebenso schnell sinken bei Wegfall der Stauung.

Es ist einleuchtend, dass die initiale Drucksteigerung im Exzitationsstadium der Narkose die obengenannte Erklärung haben muss. Sie dürfte auch allgemein bekannt sein. Die während der tiefen Narkose fortbestehende, oder besser gesagt eintretende, starke Drucksteigerung dagegen scheint nicht in dieser Weise erklärt werden zu können. Während der tiefen Narkose ist alle Muskelspannung beseitigt und dies in höherem Masse als in einem physiologischem Ruhezustand. Es ist deshalb kaum denkbar, dass die durch Muskelspannung im Beginn der Narkose hervorgerufene intrakranielle Drucksteigerung, wenn sie in Stadium der tiefen Narkose fortbesteht, diese Ursache haben kann. Sie muss eine andere Genese haben. Dass geht auch aus dem Umstand hervor, dass, wenn man die in der Narkose eintretende Drucksteigerung genau verfolgt, man nicht selten finden wird, dass die stärkste Erhöhung des Druckes deutlich in dem Moment eintritt, wo die Muskelchlaffheit und die Vertiefung der Narkose eintritt. Dies geht z. B. aus Fall 7 deutlich hervor. Wir sehen hier, dass der Druck im Exzitationsstadium zwischen 200 und 300 mm schwankt. Als aber die Narkose tiefer wird und die Muskulatur erschlafft, tritt eine weitere Erhöhung des Druckes auf 650 mm ein.

Die Drucksteigerung dauert so lange an, als die tiefe Narkose besteht. In dem Moment, wo sie oberflächlicher wird, und der Pat. erwacht, sinkt der Druck wieder ab. Der Druck sinkt nicht mit dem Aussetzen des Narkosemittels, sondern erst beim Erwachen. Fall 9 ist ein Beispiel dafür. Nach Aussetzen des Narkosemittels (Chloroform) dauert die Narkose noch 12 Min. Während dieser Zeit bleibt der Druck unverändert auf 500 mm um beim Erwachen schnell zu sinken. Fall 10 zeigt dasselbe Verhalten des Druckes. Nach Aussetzen der Ätherzufuhr dauert die Narkose noch 15 Min (imbezilles Kind). Der Druck ist während dieser Zeit unverändert 350 mm und sinkt beim Erwachen auf 100 mm.

Um ausschliessen zu können, dass die initiale exzitatorische



Drucksteigerung für die spätere Drucksteigerung mehrweniger verantwortlich ist, wird folgender Versuch gemacht.

*Fall 11.* E. A., 8 Jahre. Tuberkulöse Meningitis mit besonders starken subj. Beschwerden, die durch ausgiebige Lpt. gemildert werden. Das Kind erhält per rectum 8 g Hedonal, welches Mittel meiner Erfahrung nach den intrakraniellen Druck nicht viel beeinflusst. Nach einer Stunde, als das Kind ruhig schläft, ist der Druck bei Lpt. 150 mm. Nun wird Äther durch Inhalation zugeführt. Der Druck beginnt sofort zu steigen, obwohl keine Spur von Exzitation vorhanden ist, da das Kind bei Beginn der Ätherzufuhr ruhig schläft und die Hedonalnarkose tief genug ist, um jede Spur von Unbehagen vom Äther zu verhindern. Als die Narkose nach wenigen Minuten noch tiefer wird, steigt der Druck schnell und heftig auf 500 mm. Nach Aussetzen des Äthers sinkt der Druck auf das vorige Niveau von 150 mm, und das Kind schläft weiter.

Dieser Fall zeigt somit, dass Hedonalnarkose keine Drucksteigerung hervorruft. Ätherinhalation ruft dagegen sofort eine solche hervor, obwohl keine Exzitation eintritt, die immer eine Drucksteigerung hervorruft. Die in der tiefen Narkose auftretende Drucksteigerung hat somit mit der initialen Drucksteigerung nichts zu tun, sondern muss in anderer Weise entstehen.

In der Mehrzahl der untersuchten Fälle wurde die hier beobachtete intrakranielle Drucksteigerung während der tiefen Narkose durch Inhalationsnarkose mit Äther oder Chloroform hervorgerufen. Es wäre denkbar, dass die Inhalation des ziemlich differenten Narkosemittels durch Veränderung der Atmung irgendwie den Druck beeinflusst, weshalb auch untersucht worden ist, ob auch rektale Äthernarkose dieselbe Drucksteigerung hervorruft.

*Fall 12.* W. E., 6 Jahre. Tuberkulöse Meningitis. Lpt. ergibt einen Druck von 120 mm. Nach Abschluss derselben wird rektale Äthernarkose mit 40 g Äther in 60 g Olivenöl eingeleitet. Nach 40 Min. tiefe Narkose. Erneuerte Lpt. ergibt einen Druck von 350—400 mm. Der Druck wird 10 Min. lang beobachtet und schwankt zwischen 350 und 400 mm. Danach wird eine geringe Menge von Äther als Inhalation gegeben. Dies ruft eine schnelle Senkung des Druckes auf 240 mm hervor was durch die tiefen Atemzüge bei der Ätherinhalation verursacht ist. Nach Absetzen des Äthers geht der Druck wieder auf 400 mm zurück.

In diesem Falle wurde tiefe Narkose durch rektale Ätherzufuhr herbeigeführt. Es wurde dieselbe Drucksteigerung wie bei der

Inhalationsnarkose beobachtet. Die Art der Zufuhr des Narkosemittels scheint somit ohne Bedeutung zu sein. Die Drucksteigerung kann nicht durch abnorme Zirkulationsverhältnisse infolge Störungen der Respiration bei der Inhalationsnarkose verursacht sein. Da aber die Drucksteigerung so schnell eintritt und so stark ist, dass immerhin als wahrscheinlich anzusehen ist, dass sie trotzdem von einer abnormen Füllung der Gehirngefäße — die aber keine Stauung sondern eine mehr aktive Füllung sein muss — schien es bedeutungsvoll, eine ähnliche Beobachtung wie diejenige von CARLE und MUSSO durchzuführen, welche Verfasser einen Mann mit einem Defekt im knöchernen Schädel während der Chloroformnarkose beobachteten. Sie fanden dabei ein Einsinken des Defekts. Eine solche Gelegenheit bot sich im Jahre 1928, als ein 10-jähriger Knabe mit Pyrgozephalie aufgenommen wurde. Dieser hatte auch Knochenlücken im Schädel und unter anderem auch einen grossen Defekt am Hinterhaupt im Verlauf des Sinus longitudinalis. Beim Schreien wölbte sich Sinus haselnussförmig vor, sonst war von ihm nichts zu sehen. In diesem Falle wurde das Verhalten des Sinus während der Äthernarkose beobachtet. Es konnte festgestellt werden, dass im Exzitationsstadium — wie erwartet — eine starke Vorwölbung eintrat. Diese Vorwölbung wurde in der tiefen Narkose noch stärker, so dass der Sinus in diesem Stadium prall gefüllt war und noch mehr über die Oberfläche hervorragte. So lange die Narkose dauerte, war diese starke Füllung unverändert. Im Gegensatz zu der Beobachtung von CARLE und MUSSO, die mit Chloroform arbeiteten, konnte somit in diesem Falle eine starke Blutfüllung des Gehirns während der tiefen Narkose festgestellt werden. In diesem Zusammenhange sei nochmals auf die Versuche von ROY und SHERRINGTON hingewiesen, die in Tierversuchen fanden, dass intravenöse Zufuhr von Äther in therapeutischen Dosen eine starke Erweiterung des Gehirns hervorruft, welche wahrscheinlich durch eine Steigerung des venösen Blutdruckes bedingt ist. Dieselben Verff. fanden im Tierexperiment auch, dass Ätherinhalation zuerst eine Kontraktion und dann eine Erweiterung des Gehirns hervorrief.

Es ist auch experimentell beim Menschen nachgewiesen wor-

den, dass eine allgemeine Erweiterung der Gefässe, die einen Abfall des Blutdruckes bewirkt, gleichzeitig eine starke Erhöhung des intrakraniellen Druckes zu Folge hat. PICKERING und HESS fanden, dass eine intravenöse Injektion von Histamin in einer Menge von 0,1 mg eine gewaltige periphere Gefässerweiterung verursacht. Gleichzeitig mit dieser Gefässerweiterung tritt eine Senkung des Blutdruckes und eine starke Steigerung des Lumbaldruckes ein. Diese ist kaum anders zu erklären, als dass die Gefässerweiterung auch das Gehirn mit betroffen hat.

Wenn man an Hand der oben mitgeteilten Beobachtungen davon ausgeht, dass die Inhalationsnarkose mit Äther und Chloroform eine starke aktive Blutüberfüllung des Gehirns hervorruft, welche die beobachtete Steigerung des durch Lumbalpunktion gemessenen intrakraniellen Druckes verursacht, bleibt noch zu untersuchen, inwieweit die Narkosemittel erfahrungsgemäss Gefässerweiterungen in anderen Körperbezirken hervorrufen. IPSEN, der grundlegende Beobachtungen über das Verhalten der Hauttemperatur unter verschiedenen Bedingungen gemacht hat, untersuchte auch das Verhalten der Hauttemperatur, besonders der Füße, während der Äthernarkose. Eine kontinuierliche Messung der Hauttemperatur beider Füße während der Narkose zeigte folgendes Verhalten der Hauttemperatur. Die Normalkurve zeigt eine Hauttemperatur von 26—33° C. Gleichzeitig mit dem Einschlafen des Pat. steigt die Hauttemperatur des Fusses auf 34—36°. Die Steigerung vollzieht sich in 10—20 Min. Der Temperaturdifferenz kann bis 12° betragen. Die Steigerung der Hauttemperatur vollzieht sich beim Einschlafen, so dass man zu operieren beginnen kann, wenn die Temperatursteigerung eingetreten ist. Während der Narkose verläuft die Temperaturkurve horizontal. Die Ursache der gesteigerten Temperatur ist eine Erweiterung der Arteriolen der Haut. Beim physiologischen Einschlafen tritt auch eine, wenn auch geringere, Temperatursteigerung der Haut ein. Die Gefässerweiterung ist zentral bedingt. Wahrscheinlich tritt sowohl im Schlaf als auch während der Narkose eine zentrale Regulation ausser Funktion.

Es scheint somit, dass das Verhalten der Kapillaren und Arteriolen im Gehirn und in der Haut während der Narkose

ganz dasselbe ist. Es tritt in beiden Gebieten eine starke Hyperämie ein, obwohl im Gehirn mehr eine Hyperämie, in der Haut mehr eine gesteigerte Durchblutung zustandezukommen scheint. Hier soll auch erwähnt werden, dass STEVENSON, CHRISTENSON und WORTIS gefunden haben, dass der normale Schlaf von einer deutlichen Steigerung des intrakraniellen Druckes begleitet ist.

Hinsichtlich der sonstigen Blutverteilung während der Narkose fand SJÖSTRAND in Versuchen an Mäusen und Meerschweinchen, dass Narkose mit Äther, Chloroform und Urethan die Blutmenge in den peripheren Gefäßen auf Kosten innerer Organe, namentlich der Leber, der Nebennieren und der Milz, sowie auch in der Muskulatur steigert. Diese Steigerung kann beträchtlich werden. Dagegen riefen Somnifen und Pernocton als den Narkosemitteln verwandt keine solchen Veränderungen hervor. Die Steigerung des intrakraniellen Druckes während der Äthernarkose ist somit wahrscheinlich im Gebiet des Zentralnervensystems ein Ausdruck für die Eigenschaft dieses Narkosemittels, ausgiebige Vasodilation zu erzeugen. Diese ruft eine Zunahme des Volumens des Gehirns hervor, was zu einer starken Drucksteigerung innerhalb der Schädelkapsel führen muss.

Diese Untersuchung hat somit mit aller Deutlichkeit ergeben, dass man nicht mit normalen Verhältnissen des intrakraniellen Druckes während der Narkose rechnen kann. Die Äthernarkose ruft eine starke Steigerung dieses Druckes hervor, welche sich von der in Exzitationsstadium auftretenden vorübergehenden Steigerung unterscheidet. Im Stadium der Vollnarkose herrscht im Zentralnervensystem ein stark gesteigerter Druck, welcher im gesteigerten Druck des Liquors bei der Lumbalpunktion zum Ausdruck kommt. Diese Drucksteigerung beträgt oft mehrere hundert Prozent des präformierten Druckes und scheint immer vorhanden zu sein.

Die Ursache der während der Narkose auftretenden Drucksteigerung ist eine Hyperämie des Gehirns, die wahrscheinlich von einer Erweiterung der Arteriolen und Kapillaren hervorgerufen wird. Eine Vermehrung der Liquormenge tritt wahrscheinlich unter dem Drucke der starken Hyperämie ein. Die Erhöhung

des Druckes und dessen Senkung bei Eintritt bzw. Aufhören der Narkose verläuft aber so schnell, dass Variationen in der Menge des Liquors keine grössere Rolle spielen können. Die Veränderungen der Blutmenge des Gehirns müssen die Hauptursache der gefundenen Druckschwankungen sein. Chloroform und Chloraethyl scheinen dieselbe Druckerhöhung hervorzurufen, wie Äther während der Vollnarkose.

Äther, Chloroform und Chloraethyl haben somit eine ganz andere Wirkung auf den intrakraniellen Druck als Barbiturpräparate, welche eine Senkung des Druckes hervorrufen. Die ersteren rufen eine Hyperämie des Gehirns hervor, die letzteren eine Anämie. Avertin dagegen scheint in seiner Wirkung mehr den Inhalationsmitteln verwandt zu sein.

Es ist einleuchtend, dass man von einer Messung des Lumbaldruckes während der Narkose keinen Nutzen haben kann, wenn man beabsichtigt, die wahren Druckverhältnisse im Zerebrospinalraum festzustellen. Die körperliche Ruhe während der Vollnarkose ruft keine entsprechende Ruhe in zentralen Nervensystem hervor, sondern die Narkose geht mit einer sehr starken Hyperämie des Gehirns einher. Diese ruft eine starke Steigerung des Lumbaldruckes hervor. Die Druckmessung ist deshalb wertlos, wenn sie während der Narkose ausgeführt wird.

Früher war man bisweilen versucht, in therapeutischer Absicht eine Hyperämie des Gehirns hervorzurufen. Es wurde vorgeschlagen und auch geprüft, eine solche Hyperämie durch Abschnüren der Venen am Hals zu bewirken. Die einfachste Methode, eine starke Hyperämie im Zentralnervensystem hervorzurufen, ist die Äthernarkose. Es bleibt dahingestellt, ob man hiervon einen Nutzen haben kann. Vielleicht wäre es eines Versuches wert, die nach der Lumbalpunktion bisweilen durch Nachsickern von Liquor entstehenden Beschwerden durch Ätherinhalation zu beeinflussen. Andererseits scheint es nicht unmöglich, dass der starke Überdruck im Gehirn während der Narkose einen schädlichen Einfluss haben kann.

### Zusammenfassung.

Äthernarkose ruft eine starke Steigerung des intrakraniellen Druckes hervor. Dieselbe Wirkung haben Chloroform und Chloräthyl.

Während der Vollnarkose besteht ein Druck, der den präformierten Druck wesentlich und oft um mehrere hundert Prozent übersteigt.

Die Druckerhöhung bleibt während der Dauer der Narkose konstant. Sie wird von einer Hyperämie des Gehirns hervorgerufen, welche durch eine Erweiterung der Arteriolen und Kapillaren hervorgerufen wird. Beim Erwachen gehen die Hyperämie und die Erhöhung des Druckes schnell zurück.

Die während der Narkose durch Lumbalpunktion gefundenen Werte des Druckes sind deshalb nicht zu verwerten.

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## **Some Notes on the Development of Memory During the First Years of Life.**

By

**NILS LINDQUIST.**

As we know, memory is of enormous importance for mental life. Our whole existence depends on memory, which makes learning and cogitation possible, and forms the basis of our comprehension of the external world. It is a commonplace that memory links up the past with the present, and that any progression would be unthinkable without it.

Memory thus plays the greatest rôle in the total mental development of the infant. An absolutely definite consciousness is, however, a prerequisite for the perception of impressions.

The earliest functions of the child's memory are purely mechanical. This mechanical memory records the environment quite simply as associations between different impressions (BÜHLER). — The first display of an active memory appears when the child's play of features and its attitudes show a distinct familiarity with the persons and things continually surrounding it. At first, the retention of these impressions is of very short duration and vanishes quickly. The span of retention increases, however, with the development in general. Things observed by the child daily, and their functions, are sooner or later linked together under the influence of the senses, especially the senses of sight, hearing and touch, to so-called impression complexes. It is out of these latter that our earliest conceptions of the properties and effects of things are formed. These simple acts of memory make the raw stuff out of which thinking in the proper sense finally develops (BÜHLER). The process of recollec-



tion passes through many stages, from the first blurred impressions to the detailed act of remembering with localization and temporalization. If certain aspects of the thing to be recalled have vanished, e. g. if both localization and temporalization are lacking, only a simple recognition remains which is not determined very closely with regard to time, place, or possible other aspects. If the impression is still vaguer and forced still further back in the consciousness, we arrive at what may be called the sense of familiarity of an experience. To put it in another way the child's memory may be said to pass through a development, the main stages of which can be described as follows 1) a vague feeling of recognition, 2) a more definite recognition and 3) the complete act of remembering with localization and temporalization (BÜHLER).

The first objects at the sight of which the child experiences a feeling of recognition are very probably the faces which surround it daily, particularly that of its mother. Even within the first 6 months the child is observed to make a definite distinction between the usual environment and a strange one.

According to BÜHLER the first recognition always refers to persons and things which continually surround the child, and it is thus based on experiences which lie close together in respect of time. A short break in these time connections is, however, enough to make the nearest surroundings seem strange to the child. During the next 6 months, too, the child's memory will only extend over a couple of days, in exceptional cases over 2—3 weeks. It has been proved that complex impressions are best retained; simple impressions vanish quicker. Therefore a child will sooner recognize people, who by their looks, voice, movements and so on afford more sensory stimuli than dead things. — During the 2nd year of age the capacity of recognition develops very rapidly, and, at the end of the first 24 months, the child's memory is able to extend over nearly a couple of months. The above data are mainly based on results obtained by C. and W. STERN. In their work »Erinnerung, Aussage und Lüge in der ersten Kindheit« they treated these problems in detail, on the basis of their observations of their own three children, over whose development



of memory diaries were kept. Other authors, too, have published data on the powers of recognition of their own children, though mostly in the form of single observations (i. a. LINDNER, whose 9-month-old son recognized his father after 4 days, LIPMANN, whose 11-month-old son recognized his father after 5 days, STRÜMPFELL, whose 11-month-old daughter recognized her wet nurse after 6 days, DYROFF, whose 11-month-old daughter recognized her mother after 14 days).

My original aim was to find out how soon young children may forget their parents. But memory rather than forgetfulness came to the fore, and the present study thus deals with the child's power of simple recognition during the first years of life.

The method employed was quite simple: I registered the child's immediate reaction of recognition towards its mother — always presuming that the mother had tended the child herself. The father will not do so well as a test-object. — An 18-month-old child showed no signs of recognizing her father who came to fetch her home from the hospital. But she screamed with joy when she saw her own red coat. (The influence of affect on memory!) — When a child is about to leave the hospital, I have therefore recorded *if* and *how* the child recognizes its mother in those cases where the child has not met or seen her during its stay in hospital.

The child's memory for simple impressions was first tested with 1) its mother's voice, 2) the sight of its mother. If the results were negative on these points, a complex impression of seeing and hearing was tested: the mother goes up and speaks to the child. In the beginning of the experiment the mother is placed behind a screen and talks (she is not allowed to mention the child's name, however). If the child does not react then, the mother stands a couple of metres in front of the child, turned towards the light (she is naturally not allowed to keep her hat on). She is not to speak, but may smile at the child. If the child still shows no signs of recognition, the mother is permitted to go up to it and talk to it together with the investigator.

It is evident that a certain registration of the child's recognition *may* be difficult, and sometimes definitely uncertain,

not to say impossible. But as a rule the child lights up in quite a special way, looks steadily at its mother in spite of other persons being present, laughs in most cases, moves its legs, and breathes more rapidly. Older children begin to cry and, if they are able to talk, to call for »Mother».

We must, of course, allow for a not inconsiderable source of error in the children's varying mentality. Some children are friendly towards everyone, which may possibly combine to blur the limits for their more special expressions of joy at the sight of their mothers. Other children, of a more surly disposition, show no definite reaction towards their mother at all, even if they have recognized her. That they have done so, may become evident, when the child begins to cry as its mother leaves the room. But in such a case we cannot, of course, know for certain *which* impressions there are that have decided the recognition. — It has been pointed out (MURCHISON) that the degree of forgetfulness after varying intervals may be due to the type of occupation during the interval. If this is so, it might be probable that the type and degree of the disease for which the child has been treated in hospital were of some importance. The present small material does not allow of any conclusions in this respect, however, especially as we have to reckon with a considerable margin for individual differences.

The material is composed of 85 children aged from 6 to 36 months, and the results are summarized in fig. 1. This figure must not be regarded as a graphic representation of a statistically correct material, as the results are not directly comparable, and the distribution of the material uneven. — A plus sign in the figure denotes a positive reaction of recognition, a plus in a square represents hearing impressions, a plus in a circle visual impressions and an ordinary plus sign combined hearing and visual impressions. A minus sign indicates that the child did not show any signs of recognition. The plus signs are placed so as to mark that the child still recognizes its mother at this time. Its memory may encompass a still longer period, and here the sign thus only denotes the minimal memory of the individual. The minus signs denote that, at this time, the mother has disappeared from the child's consciousness, but this may, of



Naturally, a material such as the present does not permit any too far-reaching conclusions, but it nevertheless gives us a certain idea of the lay of the land. It proves that there are children with good memories and children with bad. We can furthermore see that a fairly large number of children between 6 and 12 months show a reaction of recognition after an interval of 8 days, and that, at the end of the first 12 months, some children have a memory which stretches over at least 3 weeks. We also get a rather good idea of the comparative value of different impressions as eliciting a reaction of recognition, as all the children (with one exception) have been tried in the same way. An ordinary plus sign, representing the complex impression, thus implies a negative reaction to simple visual and auditory impressions, and a plus in a circle tells us that the auditory impression did not elicit any response. We are, consequently, justified in stating that complex impressions are better adapted for eliciting a »reaction of recognition» than simple impressions. Another outstanding feature is that a child's visual memory appears at a considerable earlier age than its auditory memory. Even at 7 months one child was able to recognize its mother after an interval of one week. But no child in the present material could recognize its mother's voice until it was 16 months old. We therefore venture to conclude that the visual memory appears at a considerably earlier stage of development than the auditory memory.

The minus sign is, as mentioned above, placed so as to indicate that the child has already forgotten its mother at that time. Between 6 and 12 months this may occur in less than a week. But there is a considerable individual variation, and it is possible that other factors also exert an influence. It is, of course, very probable that the memories of a very ill child or a child with a painful disease may vanish more rapidly than under normal circumstances.

If, for example, we look at the 11-month-old children in the figure, there are 2, treated for acute otitis (with paracentesis) and bronchopneumonia respectively, who forgot their mothers already after 5 and 6 days respectively, while a couple of other children, treated for eczema with painful itching and gastro-

enteritis with eclampsia respectively, showed a definite reaction of recognition even after 3 weeks. All these 4 children had thus been treated for painful and grave diseases, and the individual variations seem to have played the greatest rôle in these cases.

A 31-month-old child was treated for 11 days in hospital for asthmatic bronchitis and bronchopneumonia. At the beginning of her stay in hospital the child pined very much for her mother, but showed no signs of recognition whatsoever when fetched by her. There is, of course, a possibility that the exceptionally rapidly vanishing memory of this child may be connected with her severe disease. But on the other hand, the two 12-month-old children, who after 7 days still showed a definite recognition of their mothers, had both been treated for bronchopneumonia. As I have pointed out above, the present material is too small to warrant any conclusions as to the possible influence of disease on the memory.

The results may be summarized as follows: Small children show a power of recognition, extending over several days, already at about 6 months. This power of recognition then increases rapidly to encompass an interval of at least 3 weeks at the end of the first 12 months, anyhow as far as concerns the recollection of complex impressions. Simple impressions as elicitors of a reaction of recognition seem to demand a somewhat higher age, but appear to elicit responses at least during the 8th month — this refers especially to visual impressions. We seem further to be justified in stating that the visual memory develops considerably earlier than the auditory memory, which latter is not conspicuous in the present material until the age of 18 months.

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AUS DER PÄDIATRISCHEN KLINIK DES KAROLINISCHEN INSTITUTS IM  
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UND DEM »SACHS'SCHEN KINDERKRANKENHAUS«, STOCKHOLM  
(CHEF: DOCENT J. HENNING MAGNUSSON).

## **Über die Anwendung eines Aminosäurengemisches (Kaseinhydrolysat) als Zusatznahrung für Frühgeborene während der ersten Lebenswochen.**

Von

**J. HENNING MAGNUSSON.**

Die Frühgeburten weisen neben ihren geringen Längen- und Gewichtsmassen noch eine ganze Reihe charakteristischer Züge auf, die sich je nach dem Grade des Nichtausgetragenseins mehr oder minder deutlich bemerkbar machen. Bald nach der Geburt machen diese Kinder oft den Eindruck einer verhältnismässig guten Lebenskraft. Die Unreife kommt aber binnen kurzem in mannigfachen Erscheinungen von grösserer oder geringerer Bedeutung für den Zustand der Kinder zum Ausdruck. Nach wenigen Tagen liegen namentlich die kleinsten von ihnen ständig in einen tiefen Schlaf versunken, ohne sich zu bewegen und ohne anders als ganz ausnahmsweise irgendeinen Laut von sich zu geben. Diese funktionelle Insuffizienz ist jedoch in der Regel eine vorübergehende, und die Schwächezeichen lassen Schritt für Schritt nach, um nach längerer oder kürzerer Zeit zu verschwinden.

In den ersten Lebenstagen bzw. -wochen kann die Pflege eines solchen Kindes mancherlei Schwierigkeiten bieten. Wenn man von den häufigen Komplikationen durch intrakranielle Verletzungen und Infektionen absieht, macht sich die funktionelle Schwäche vor allen Dingen in gewissen Beziehungen auf augenfällige Weise geltend, in der Wärmeregulation, Herztätigkeit, Atmung und Ernährung. Den Wärmebedarf können wir heutzutage einigermassen befriedigend decken und regeln. Das gleiche gilt für die

Störungen der Herztätigkeit und diejenigen der Atmung mit den sog. apnoischen Zuständen, unter der Voraussetzung, dass ihre Ursache nicht in einer intrakraniellen Blutung oder einer anderen Affektion von ähnlicher Tragweite liegt. Die Ernährung dagegen ist unter vielen Gesichtspunkten ein komplizierteres und schwerer lösbares Problem.

Einigkeit herrscht bezüglich der Überlegenheit der Frauenmilch bei der Ernährung von Frühgeburten, und ohne zwingende Gründe wird kein derartiges Kind der Gefahr ausgesetzt, welche eine künstliche Nahrung mit sich bringen kann. Die Fütterung mit Frauenmilch scheint tatsächlich eine der Voraussetzungen für eine niedrige Mortalität innerhalb dieser Gruppe von Kindern zu sein. Auf der anderen Seite hat das nicht ausgetragene Kind in der Regel sein extrauterines Leben wesentlich verfrüht beginnen müssen, und die Frauenmilch kann daher für dasselbe nicht in demselben Grade als Idealnahrung gelten wie für das ausgetragene. Bei der Ernährung der Frühgeburten stossen wir auch auf Schwierigkeiten, mit denen wir bei ausgetragenen Kindern nicht zu rechnen brauchen, wenn es sich darum handelt, ihnen Nahrung in hinreichender Menge zuzuführen. Dies trifft ganz besonders für die kleineren Kinder mit einem Geburtsgewicht von beispielsweise 1 500 g oder darunter zu. Den Kalorienbedarf dieser Kinder durch Zufuhr lediglich von Frauenmilch mit ca. 70 Kalorien pro Deziliter zu befriedigen, stellt grosse Anforderungen nicht nur an das Fassungsvermögen des Magens, sondern auch an die Verdauungsorgane und den Stoffwechselapparat in seiner Gesamtheit. Hierzu kommt noch, dass wir wenigstens während der ersten Lebenswochen eine schlechte oder jedenfalls nicht ganz gute Funktion des Verdauungsapparats zu erwarten haben.

Jede Frühgeburt stellt gewissermassen ein Ernährungsproblem für sich dar. Nicht selten fehlen bei den kleinsten derselben in der ersten Lebenszeit sowohl Saug- wie Schluckreflexe. Sie müssen da mit einer Sonde gefüttert werden, was ein schonender und leicht zu bewerkstelligender Eingriff ist, namentlich da auch Brechreflexe oft nicht vorhanden sind. Die Nahrungszufuhr mit der Sonde ist auch in anderen Situationen die Methode der Wahl,



z. B. wenn das Kind zu schwach ist, um mit einem Sauger zu trinken, wenn es sich erbricht oder bei der Fütterung zyanotisch wird. Durch die Sondenernährung wird ausserdem die Dauer der Mahlzeiten und damit der Kontakt mit dem Pflegepersonal auf ein Mindestmass beschränkt. Auf diese Weise wird die Gefahr einer Infektion des Kindes durch das Pflegepersonal geringer.

Während der ersten Tage können nur kleine Mengen Frauenmilch zugeführt werden. Man scheint auch über die Notwendigkeit einig zu sein, sich zunächst bei der unteren Grenze des Nahrungsbedarfs zu halten und Überfütterung ebenso sorgfältig zu vermeiden wie Unterernährung. Das Mahlzeitquantum wird nur langsam erhöht, und zwar um so vorsichtiger, je weniger das Kind wiegt und je unreifer es ist. Im besonderen muss man bei solchen Erscheinungen, wie Erbrechen und Zyanose im Anschluss an die Fütterungen, grosse Vorsicht walten lassen. Bei den weiteren Zulagen richtet man sich nach Gewicht und Nahrungstoleranz des Kindes. Wegen der Neigung zu akuter Inanition wird die regelmässige Nahrungszufuhr frühzeitig eingeleitet, binnen der ersten 12 Stunden nach der Geburt. Zum Ausgleich des Flüssigkeitsverlustes durch die Nieren, Darmentleerungen, Lungen und Haut wird ausserdem an den ersten Lebenstagen Flüssigkeit in Form von abgekochtem Wasser per os oder Ringerscher Lösung subkutan zugeführt.

Bei Ernährung mit Frauenmilch allein verläuft nicht selten die Gewichtskurve nach dem initialen Gewichtsfall während der drei oder selbst vier ersten Lebenswochen nahezu waagrecht. Danach setzt allerdings ein regelmässiger Anstieg ein, vorausgesetzt, dass keine Komplikationen in Form von Infektionen od. dgl. auftreten.

Es sind Versuche gemacht worden, die Kaloriezufuhr auf verschiedene Weise durch Zusatznahrung neben der Frauenmilch zu erhöhen. In der Regel hat man kleine Mengen von einem konzentrierten Kuhmilchgemisch gegeben, vor allem in der Absicht, den grossen Eiweiss- und Salzbedarf zu decken. Andere haben Kasein oder Glykose zugeführt, beziehungsweise diese beiden Mittel kombiniert. Man scheint darüber einig, dass eine derartige Zusatznahrung erst dann verwendet werden darf, wenn die 2—3



ersten Lebenswochen gut überstanden sind. YLPPÖ gibt, um ein Beispiel anzuführen, von der 4.—5. Lebenswoche an zur Frauenmilch eine Zulage von Kuhmilch + 10 % Zucker in einer Menge, die 10 % der gesamten Nahrungsmenge nicht übersteigt. HESS steigert den Proteingehalt der Kost, indem er ein gewisses Quantum der Frauenmilch durch »skimmed lactic acid milk« ersetzt.

Aus rein theoretischen Gründen kann man damit rechnen, dass die Eiweisskörper für die Ernährung des frühgeborenen Kindes von allergrösster Bedeutung sind. In erster Linie müssen die durch den Stoffwechsel verbrauchten Körperproteine ersetzt werden, und ausserdem sind Eiweisstoffe zum Wachstum notwendig. Die Untersuchungen, welche SCHOENHEIMER und dessen Mitarbeiter unter Verwendung von Isotopen des Stickstoffs und Kohlenstoffs angestellt haben, machen den lebhaften Austausch ersichtlich, der in den Proteinen der Leber, des Darms und der Muskeln vonstatten geht, und der eine kontinuierliche Zufuhr von Eiweisskörpern oder wenigstens von den essentiellen Aminosäuren erforderlich macht. Für die neugeborene Frühgeburt können erhebliche Schwierigkeiten erwachsen, wenn sie ihrer Nahrungszufuhr aus dem Blutstrom der Mutter beraubt ist. Die intrauterine Nahrung besteht aus den im Blut enthaltenen Aminosäuren. Im extrauterinen Leben erfolgt die Ernährung in praxi nur mit ungespaltenem Eiweiss. Freilich enthalten sowohl Kolostrum wie Frauenmilch freie Aminosäuren (GIAUME, SPIRITO). Der Gehalt an diesen ist jedoch so geringfügig, dass er vom Standpunkt der Praxis belanglos ist.

Es ist keineswegs überraschend, dass Frühgeburten die Eiweisskörper der Nahrung schlecht ausnutzen und oft trotz beträchtlicher Eiweisszufuhr keine nennenswerte Gewichtszunahme aufweisen. Man hat auch Grund zu der Vermutung, dass Kinder in diesem Entwicklungsstadium zumindest in den ersten Lebenswochen einen mangelhaften Enzymmechanismus haben und dadurch nicht imstande sind, die gewöhnliche Nahrung ganz zu verwerten. Unter diesen Umständen würde die häufig unbefriedigende Zunahme während der ersten Zeit ein Ausdruck der Unterernährung sein. Es erschien daher ganz natürlich, diesem

jungen Organismus ein Aminosäurengemisch zuzuführen, dass alle essentiellen Aminosäuren enthält. Da die Aminosäuren vom Darm leicht absorbiert werden, dürfte die perorale Verabreichung ebenso gut ihren Zweck erfüllen, wie die von ELMAN und dessen Mitarbeitern eingeführte intravenöse Ernährung mit Aminosäuren beim Erwachsenen.

Ein derartiger, von mir vorgenommener Versuch hat sich als erfolgreich erwiesen. Wenn die Frühgeburten zu gebende Frauenmilch durch ein Gemisch von freien Aminosäuren und Polypeptiden, das sämtliche im Kasein vorkommende Aminosäuren enthält, ergänzt wurde, reagierten die Kinder regelmässig mit einer unmittelbaren Gewichtszunahme. Nach Erfahrungen bei gewissen Fällen hat es geradezu den Anschein, als würden die Aminosäuren quantitativ zur Eiweissynthese verwertet, denn die tägliche Mehrzunahme bei Zufuhr derselben entsprach ungefähr dem berechneten Gewichtsanstieg, der sich durch Eiweissaufbau und Bindung der entsprechenden Wassermenge ergeben würde. Ein Versuch mit dieser Behandlung wurde speziell während der ersten Lebenswochen für angezeigt gehalten, ehe noch der lebensunreife Organismus eine einigermaßen genügende funktionelle Kapazität erreicht hat. Die Versuchsergebnisse bei diesen Untersuchungen waren eindeutig: während der Perioden, in welchen neben der Frauenmilch Aminosäurengemisch zugeführt wurde, war die Gewichtszunahme wesentlich grösser.

Das Schrifttum enthält nur wenige Angaben über Untersuchungen des Aminosäureumsatzes bei Frühgeburten. Nach GOEBEL ist bei diesen die Aminosäurenfraktion im Harn grösser als bei ausgetragenen Kindern. Der Gehalt des Blutes an Aminosäurestickstoff war laut Angabe dieses Autors bei Säuglingen, unter diesen nur zwei Frühgeburten, und älteren Kindern der gleiche. LICHTENSTEIN fand, dass der Gehalt des Nabelschnurblutes an Aminosäurestickstoff um so höher war, je vorzeitiger die Geburt des Kindes stattgefunden hatte.

In der Klinik hat man sich erst in den letzten Jahren für die Abbauprodukte des Eiweisses in grösserem Umfang zu interessieren begonnen, und man hat auch die Frage der Zufuhr von Aminosäuren eingehender geprüft. Der Gedanke einer Be-

handlung mit Aminosäuren ist aber durchaus nicht neu. Versuche in dieser Richtung sind schon früher unternommen worden. So haben RIBADEAU-DUMAS und FOUET bereits 1924 die parenterale Verabreichung einer aminosäurehaltigen Lösung bei atrophischen Kindern empfohlen. Man verwendete eine 3%ige Lösung von aus Kuhmilchkasein gewonnenen Aminosäuren. Anfangs wurden diese in einer isotonischen Glykoselösung suspendiert, später in einem besonderen, zum Teil enteimissten Serum. LESNÉ und RICHET (1924) gaben atrophischen Kindern täglich Tropfeinläufe mit einem Serum, das 4 % Glykose, 0,7 % Kochsalz und 4 % Aminosäuren enthielt. NITSCHKE (1928) behandelte mit gutem Erfolg einen typischen Fall von Lipoidnephrose mit einem Aminosäurengemisch. In den letzten Jahren sind, seitdem ELMAN und dessen Mitarbeiter mit intravenöser Zufuhr von Eiweißhydrolysaten zu experimentieren begonnen hatten, auch auf dem Gebiet der Kinderheilkunde eine Reihe von einschlägigen Arbeiten veröffentlicht worden. Es haben — um einige Beispiele anzuführen — SHOHL und Mitarbeiter 7 Kindern ein Aminosäurengemisch sowohl peroral wie intravenös während kürzerer Zeitabschnitte verabfolgt und in sämtlichen Fällen eine positive Stickstoffbilanz erhalten. FARR hat die Wirkung der Aminosäurezufuhr beim nephrotischen Syndrom im einzelnen studiert. HILL gab gegen Milchnahrung allergischen Kindern mit gutem Resultat ein Aminosäurengemisch.

Irgendeine Angabe über Zufuhr von Aminosäurengemischen bei Frühgeburten habe ich im Schrifttum nicht finden können. Praktisch sämtliche Versuche, die Assimilation der Milch bei der Säuglingsernährung zu erleichtern, hatten das Ziel gehabt, die mit dem »curding process« verknüpften Übelstände auszuschalten. So haben u. a. BLATT, HARRIS, JACOBS und ZELDES die Behandlung der Milch vor dem Pasteurisieren mit Pankreasenzymen vorgeschlagen, wodurch die »curding tension« reduziert wird, ohne dass eine nachweisbare Hydrolyse der Eiweißkörper in der Milch erfolgt. Die von diesen Autoren bei Ernährung mit einer auf diese Weise behandelten Milch (Enzylac) erzielten Resultate sind durchweg gut.

*Eigene Untersuchungen.*

Als Aminosäurenpräparat wurde ein Kaseinhydrolysat zur intravenösen Ernährung verwendet, das in der chemischen Abteilung des Karolinischen Instituts von Laborator E. JORPES und Amanuensis K. A. J. WRETLIND ausgearbeitet worden war.<sup>1</sup> Das Milchkasein wurde durch isoelektrische Fällung und zweimalige Extraktion mit siedendem Alkohol gereinigt, wodurch Salze, Fette und Vitamine entfernt wurden. Die enzymatische Hydrolyse wurde bei 37° C durch mit Azeton entwässertes Pankreas oder einen Glycerolextrakt aus Schweinepankreas bewerkstelligt. Die Vollständigkeit der Hydrolyse wurde analytisch kontrolliert (van Slyke). Die Aminosäuren und die niederen Polypeptide wurden mittels einer neuen, von WRETLIND ausgearbeiteten Dialysetechnik von dem ungespaltenen Eiweiss getrennt. Das Präparat enthält 80—85 % freie Aminosäuren. Da die Ausbeute bei der Darstellung 80—100 % des Ausgangsmaterials beträgt, kann man davon ausgehen, dass der Aminosäuregehalt derselbe ist wie im Kasein. Die Fähigkeit, eine Anaphylaxie zu erzeugen, hat sich nicht nachweisen lassen (WRETLIND).

Wo es sich um den Gebrauch des Präparats als Zusatznahrung für Frühgeburten handelte, wurde es mit Glykose versetzt, um den Kaloriewert des Gemisches zu steigern. Um einen etwaigen Salzbedarf zu decken, wurde ausserdem eine vollwertige Salzmischung zugesetzt. Die Zusammensetzung dieser »Aminosol-Glykose« ist folgende: Aminosäurengemisch 25 %, Glykose 25 %, Salzmischung 1,5 %.

Dieses Präparat ist so konzentriert, dass es sich in unverdünnter Form nicht für die Kinder eignet. Es wurde daher in Frauenmilch bzw. während der ersten Lebenstage in Frauenmilch + abgekochtes Wasser gegeben. Auf diese Weise stellt man eine Verdünnung von in der Regel 1 : 20 her; höher als 1 : 10 durfte die Konzentration nicht sein. Das Präparat wurde gewöhnlich während der ersten Tage bzw. Wochen mit einer Sonde zugeführt, später peroral. Die perorale Darreichung bereitete bei

<sup>1</sup> Das Präparat wird unter dem Namen »Aminosol« von Vitrum, Stockholm, hergestellt.

den Frühgeburten im allgemeinen keine Schwierigkeiten und liess sich stets durchführen. Dies gilt namentlich für diejenigen Kinder, die das Präparat von Anfang an erhalten hatten. Wenn es sich um ältere Kinder handelt, dann ist der Sachverhalt in gewisser Beziehung ein anderer. Bei vielen einschlägigen Fällen, bei denen die perorale Aminosäurezufuhr versucht wurde, machte sich infolge des Geschmacks eine Widerwilligkeit geltend. Auffällig ist aber, dass nicht wenige älteren Kinder die Aminosäuren in Form von Trockenpulver ohne Schwierigkeiten per os einnehmen konnten.

Die Frage der zweckmässigsten Dosierung des Präparats lässt sich vorderhand noch nicht erschöpfend beantworten. Es sind Versuche mit sehr wechselnden Mengen gemacht worden. Nach Zufuhr grosser Quantitäten kommt es nicht selten zu Erbrechen, meistens jedoch nur als kleinere Regurgitationen. Anzeichen von Verdauungsstörungen machten sich aber bei der Mehrzahl der Fälle nicht bemerkbar. Eine Dosis von 10 ml Aminosol-Glykose (2,5 g Kaseinhydrolysat) pro kg Körpergewicht und Tag konnte mit Ausnahme der allerersten Lebensstage praktisch jedesmal gegeben werden, ohne dass sich irgendwelche Beschwerden, wie Erbrechen oder Verdauungsstörungen, eingestellt hätten. Diese Dosierung dürfte allerdings in gewissen Fällen unnötig hoch sein, da sie eine extrem grosse Gewichtszunahme bewirkt. In zahlreichen Fällen hat sich auch die Zufuhr einer nur halb so grossen Menge als durchaus genügend zur Erzielung eines befriedigenden Gewichtsanstiegs erwiesen.

Die ersten Versuche wurden im November 1943 ausgeführt. Seitdem bin ich in der Lage gewesen, fast 150 Fälle entweder periodisch oder kontinuierlich längere Zeit hindurch zu behandeln. Interesse besass in erster Linie die Erforschung des Effekts der Aminosäurezufuhr während der ersten Lebenswochen. Hier ist aus den oben angeführten Gründen die Schwierigkeit, durch Ernährung mit Frauenmilch allein eine befriedigende Gewichtszunahme zu erzielen, am grössten. Um die hohe Variabilität, mit der wir in diesem Lebensalter stets zu rechnen haben, soweit tunlich, zu eliminieren, wurden die Versuche so angestellt, dass ein und dasselbe Kind abwechselnd Frauenmilch allein und Frauen-

milch + Aminosäurengemisch erhielt. Auf diese Weise bot sich eine Möglichkeit, die Wirkung beurteilen zu können, ohne dass das Material deshalb besonders gross sein müsste.

### *Intermittierende Behandlung.*

Der erste Bericht über die Resultate dieser intermittierenden Aminosäurenbehandlung wurde bei der Sitzung des Physiologischen Vereins in Stockholm am 10. März 1944 erstattet, und Mitteilungen hierüber sind später veröffentlicht worden (9). Die folgenden Fälle dürften daher genügen, um den Sachverhalt hier zu illustrieren.

*Fall 1.* Nr NS 50/44. ♂, 3 Wochen vor dem berechneten Zeitpunkt geboren. Geburtsgewicht 1700 g. Eltern gesund, Schwangerschaftsverlauf o. B., Entbindung normal. Im Anschluss an den Partus bekam das Kind 2,5 mg K-Vitamin und wurde dann in eine Kinderabteilung verlegt.

Bei der Aufnahme dort Untertemperatur ( $35,2^{\circ}$ ), aber sonst keine Besonderheiten. Prothrombinindex 45, weshalb K-Vitamin weitergegeben wurde. Das Kind entwickelte sich gut, erhielt während der 1. und 2. Woche Vitamin D<sub>2</sub> in zwei Stössen von zusammen 500 000 Einheiten. Der Hämoglobingehalt des Blutes war bei der Aufnahme 134 %, bei der Entlassung 87 %. Im Alter von 6 Wochen wurde das Kind als reines Brustkind mit einem Gewicht von 2420 g nach Hause entlassen. Die Einzelheiten bezüglich Ernährung und Gewichtszunahme werden aus Abb. 1 ersichtlich.

Sämtliche Fälle, die intermittierend behandelt worden waren, wiesen in den Perioden, wo sie Zulagen von Kaseinhydrolysat erhielten, eine grössere Gewichtszunahme auf als bei lediglich Frauenmilch. Der Unterschied war nicht immer so ausgeprägt wie bei dem vorstehend angeführten Fall 1. Dieser Versuch ist deshalb als Beispiel gewählt worden, weil sich die Milchmenge in den verschiedenen, zum Vergleich dienenden Zeitabschnitten einigermaßen konstant halten liess. Ferner hat dieses Kind Frauenmilch in so reichlicher Menge bekommen, dass man von weiterer Nahrungszufuhr keinen nennenswerten Effekt erwarten würde, unter der Voraussetzung, dass das Kind jene hätte ausnutzen können. Trotzdem ist der Unterschied zwischen den Perioden mit und ohne Aminosäurezulage erheblich.

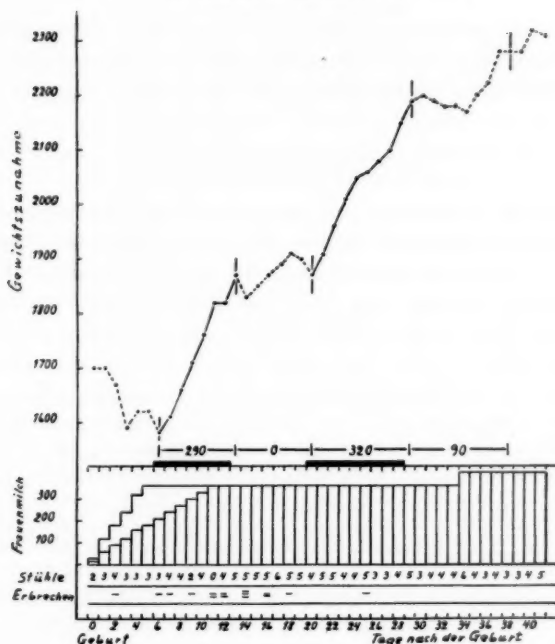


Abb. 1. In der Gewichtskurve bezeichnet  $\bullet - - - \bullet$  Perioden, während der das Kind nur Frauenmilch erhalten hatte und  $\bullet - - - \bullet$  Perioden mit Frauenmilch + Aminosol-Glykose. Die Zahlen zwischen den senkrechten Strichen unterhalb der Gewichtskurve geben die Gewichtszunahme während der verschiedenen Perioden (2 siebentägige und 2 neuntägige Perioden) an.  $\text{—}$  = Aminosol-Glykose in einer Dosis von täglich 10 ml (2,5 g Aminosäurengemisch) pro kg Körpergewicht als Zusatznahrung.

Man kann immerhin nicht ohne weiteres behaupten, der grössere Gewichtsanstieg während der Perioden mit Aminosol-Glykose sei beweisend für die Wirkung gerade des Aminosäurengemisches, wenn es auch vom physiologischen Standpunkt selbstverständlich erscheint, dass dies der Fall sein muss. Man könnte einwenden, dass den Kindern während dieser Zeitabschnitte eine grössere Anzahl Kalorien zugeführt werde, und dass sie eben deshalb mehr zunehmen. Um diesen Punkt zu klären, wurden in einer Fallserie ein Vergleich angestellt zwischen Zulage von



Aminosol-Glykose und Zulage eines Gemisches, das unverdautes Kasein, Glykose und Salze in denselben Konzentrationen und Mengenverhältnissen enthielt wie jenes Mittel. Der Kaloriengehalt dieses Gemisches ist derselbe wie bei Aminosol-Glykose. Der einzige Unterschied ist der, dass das Aminosäurengemisch durch unverdautes Kasein ersetzt ist. Der folgende Fall sei zur Veranschaulichung eines derartigen Versuchs angeführt.

*Fall 2.* Nr S 669/44. ♂, 2 Monate vor dem berechneten Zeitpunkt geboren. Geburtsgewicht 1 640 g, Länge 43 cm. Mutter gesund, Erstgebärende, Schwangerschaftsverlauf o. B., normale Entbindung. Im Anschluss an den Partus bekam das Kind 10 mg K-Vitamin und wurde etwa eine Stunde später in eine Kinderabteilung verlegt.

Bei der Untersuchung dort hatte das Kind eine gute Farbe und einen guten Tonus, schrie aber schwach und hatte eine leichte Untertemperatur ( $35,5^{\circ}$ ). Unterhautfett spärlich, innere Organe o. B., Prothrombinindex 110, am 4. Tage leichter Ikterus, der bald verschwand. Das Kind, das von Anfang an ins Bett gelegt wurde, hatte in den 3 ersten Wochen eine etwas ungleichmässige Temperatur, dann aber Monothermie von  $37^{\circ}$ . Vom 20. bis zum 33. Tage leichter Schnupfen ohne sonstige nachweisbare Erscheinungen einer Infektion. Der Allgemeinzustand war die ganze Zeit gut, keine Zyanoseanfälle, keine Ödeme, niemals Durchfall. Der Hämoglobingehalt des Blutes betrug am 2. Tage 110 %, am 56. Tage 64 %. Röntgenuntersuchung der Handknochen im Alter von 2 Monaten: keine Anzeichen von Rachitis. Einzelheiten der Ernährung und Gewichtszunahme siehe Abb. 2.

Bei sämtlichen Experimenten, in denen wie bei dem vorstehend wiedergegebenen Fall 2 Aminosol-Glykose und ein Gemisch von Kasein, Glykose und Salzen miteinander verglichen wurden, ergab sich während der Perioden mit Aminosol-Glykose eine wesentlich grössere Gewichtszunahme. Die den Kindern durch die Zusatznahrung zugeführte Kalorienmenge ist bei beiden Mitteln dieselbe. Die Mehrzunahme während der Perioden mit Kaseinhydrolysat lässt sich infolgedessen nicht durch eine Steigerung der Kalorienzufuhr in diesen Zeitabschnitten erklären. Die Ursache derselben ist in der Zufuhr eben der Aminosäuren zu suchen, da die verabreichten Glykose- und Salzmengen während der verschiedenen Vergleichszeiten ebenfalls gleich waren.

Um diesen Punkt weiterhin zu beleuchten wurde eine Serie Versuche ausgeführt, bei denen Glykose und Salzgemisch wegge-



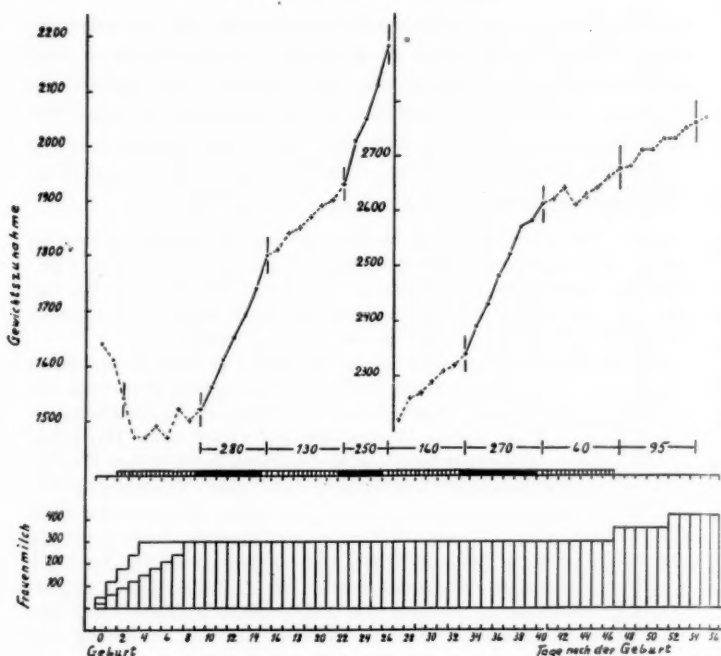


Abb. 2. In der Gewichtskurve bezeichnet + - - - - - Perioden von 7 Tagen, während der das Kind eine aus unverdaulichem Kasein + Glykose + Salze bestehende Zusatznahrung erhalten hatten.  $\square \square \square \square \square \square \square$  = Zusatznahrung von Kasein + Glykose + Salzgemisch (dieselben Konzentrationen und Mengenverhältnisse wie in Aminosol-Glykose) in einer Dosis von täglich 10 ml (2,5 g Kasein) pro kg Körpergewicht. Dauer der ersten und zweiten Periode mit Aminosol-Glykose nur 6 bzw. 4 Tage, sämtlicher übriger Perioden 7 Tage.

lassen und reines Kasein mit einem aus demselben Kaseinpräparat hergestellten Aminosäurengemisch verglichen wurde. Auch diese Experimente resultierten in einer durchweg grösseren Gewichtszunahme für die Perioden mit Kaseinhydrolysat. Es liegt m. a. W. auf der Hand, dass der Organismus des frühgeborenen Kindes in einem frühen Altersstadium nicht imstande ist, unter allen Umständen unverdautes, in Form von Kasein zugeführtes Eiweiss restlos auszunutzen. Aus diesen Versuchen geht auch hervor, dass es die Aminosäuren sind, nicht der Zusatz von Glykose bzw. Salz-

gemisch, welche bei dem Gewichtsanstieg den Ausschlag geben. Der folgende Fall mag zur Verdeutlichung der Versuchsergebnisse dienen.

*Fall 3.* Nr S 877/44. ♂, 8 Wochen vor dem berechneten Zeitpunkt geboren. Geburtsgewicht 1440 g, Länge 41 cm. Eltern gesund, Mutter 28 Jahre alt, Erstgebärende, wiederholte Blutungen während der Schwangerschaft, spontane Geburt in Steisslage. Im Anschluss an den Partus bekam das Kind 10 mg K-Vitamin und wurde dann in die Kinderabteilung verlegt.

Bei Untersuchung dort einige Stunden später hatte das Kind eine gute Farbe, fühlte sich aber schlaff an, bewegte sich wenig, schrie schwach und hatte Untertemperatur ( $33,3^{\circ}$ ). Unterhautfett spärlich, Hoden im Leistenkanal, innere Organe o. B., Prothrombinindex 90. Das Kind lag während der 10 ersten Tage in einer Couveuse und konnte dann im Bett mit elektrisch geheizter Bettdecke die Körperwärme verhältnismässig gut aufrechterhalten. Vom 10. bis zum 27. Tage hatte das Kind einen leichten Schnupfen ohne andere Anzeichen einer Infektion. Der Allgemeinzustand war die ganze Zeit gut, keine Zyanoseanfälle, keine Ödeme, nie Durchfall. Das Kind wurde während der 3 ersten Wochen mit der Sonde gefüttert, trank dann gut mit Sauger und wurde in der 5. Woche zum ersten Mal an die Brust gelegt. Gegen Ende der 1. Woche erhielt das Kind Vitamin D, in Stössen von zusammen 500 000 Einheiten. Der Hämoglobingehalt des Blutes betrug am 2. Tage 136 %, am 39. Tage 76 %. Das Kind wurde in gutem Zustand entlassen; es bekam zuletzt die Brust 6mal in 24 Stunden. Alle Einzelheiten bezüglich Ernährung und Gewichtszunahme gehen aus Abb. 3 hervor.

Ob man sämtlichen Frühgeburten während der ersten Lebenszeit Aminosäuren geben soll oder nur denjenigen, welche bei Frauenmilch schlecht zunehmen, darüber lässt sich natürlich streiten. Dasselbe gilt für die Frage, wie lange die Zufuhr von Kaseinhydrolysat fortzusetzen sei. Wird ein Kind jede zweite Woche mit Aminosäuren und dazwischen mit unverdaulichem Kasein in entsprechenden Mengen behandelt, dann ist in der Regel der Unterschied hinsichtlich der Gewichtszunahme zugunsten der Aminosäurenperioden während der ersten Zeit sehr gross. Gegen Ende des 2. Monats, um einigen bestimmten Fällen mit niedrigem Geburtsgewicht ein Beispiel zu entnehmen, wird diese Differenz kleiner. Es ist m. a. W. offenbar, dass die Aminosäurezufuhr vor allem im frühesten Lebensalter wertvoll ist.

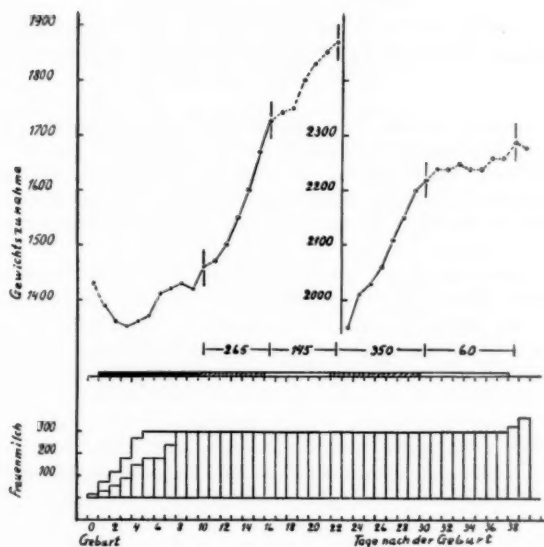




Abb. 3. In der Gewichtskurve bezeichnet o — o — o Perioden, während der das Kind als Zusatznahrung das Aminosäurengemisch (Aminosol) erhalten hatte. o — — — o — — — o bezeichnet Perioden mit Zusatznahrung von Kasein.  = Aminosäurengemisch (Kaseinhydrolysat) in einer Dosis von 2,5 g pro kg Körpergewicht und Tag,  = unverdautes Kasein in derselben Dosierung. Von den vier miteinander verglichenen Perioden dauerten die beiden ersten je 6, die beiden letzten je 8 Tage.

### Kontinuierliche Behandlung.

Zur Zeit sind Versuche mit kontinuierlicher Aminosäurezufuhr während der ersten Wochen bis zu dem Zeitpunkt, an dem das Kind an die Brust gelegt wird, im Gange. Aus technischen Gründen muss die Behandlung gewöhnlich unterbrochen werden, wenn das Kind gelernt hat, an der Brust zu trinken. Die folgenden Beispiele können angeführt werden, um die Wirkung einer derartigen Behandlung im Einzelfalle zu erläutern.

Fall 4. Nr ABB 3436/44. ♂, 5 Wochen vor dem berechneten Zeitpunkt geboren. Geburtsgewicht 1220 g. Vater gesund, Mutter schwere Albuminurie während der letzten Schwangerschaftsmonate. Entbindung normal. Im Anschluss an den Partus bekam das Kind 10 mg K-Vitamin

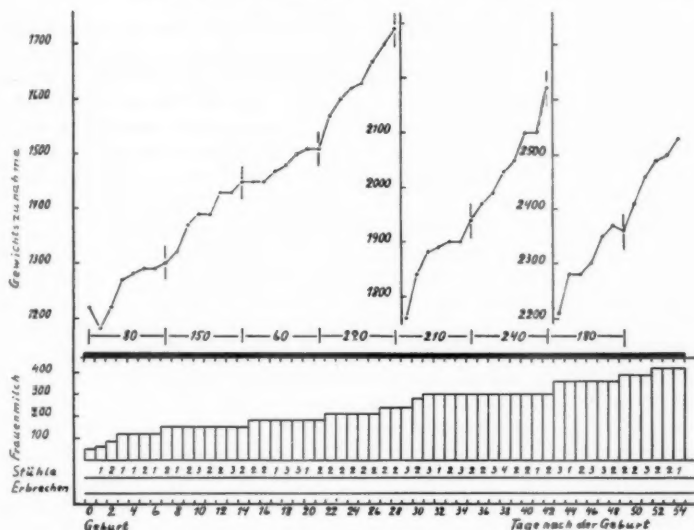


Abb. 4. Gewichtszunahme einer Frühgeburt während der 7 ersten Lebenswochen bei kontinuierlicher Behandlung mit Aminosol-Glykose.

als Injektion und wurde nach etwa einer Stunde in eine Kinderabteilung verlegt.

Bei der Aufnahme dort gute Farbe und guter Tonus, aber schwaches Schreien und Untertemperatur ( $35^{\circ}$ ). Unterhautfett spärlich, innere Organe o. B., Prothrombinindex 92. Am 5. Tage mässiger Ikterus, der bald verschwand. In den ersten Tagen (Couveuse) ungleichmässige Temperatur, später die ganze Zeit Monothermie von  $37^{\circ}$ . Während der ganzen Zeit keine Infektionen, Allgemeinzustand gut, keine Zyanoseanfälle, Ödeme oder Durchfall. Stossdosis von Vitamin  $D_2$  (500 000 Einheiten). Der Hämoglobingehalt des Blutes betrug am 4. Tage 119 %, am 54. Tage 63 %. Bei der Entlassung (am 54. Tage) befand sich das Kind in einem ausgezeichneten Zustand und wies keinerlei Krankheitszeichen auf. Die Einzelheiten hinsichtlich Ernährung und Gewichtszunahme werden aus Abb. 4 ersichtlich. Wegen der Krankheit der Mutter konnte dieses Kind erst im Alter von 6 Wochen an die Brust gelegt werden.

Auch zwei Gruppen von Drillingen verdienen Erwähnung. Die Ergebnisse der bei diesen Fällen vorgenommenen Versuche sind geeignet, die Wirkung der kontinuierlichen Behandlung weiterhin zu verdeutlichen.

*Drillinggruppe 1.* Die Eltern der Kinder waren gesund, Mutter 29 Jahre alt, Erstgebärende, Schwangerschaftsverlauf o. B. Partus 6 Wochen vor dem berechneten Zeitpunkt, spontane Entbindung mit Drilling 1 in Kopflage, 2 und 3 in Steisslage. Alle drei Kinder waren bei der Geburt in gutem Zustand. *Kind 1 und 2 waren mit allergrösster Wahrscheinlichkeit eineiig.* Die Kinder wurden, kaum 24 Stunden alt, in eine Kinderabteilung verlegt. Aus den dortigen Krankenblättern folgende Einzelheiten:

*Drilling 1.* Nr NS 447/44. ♂, Geburtsgewicht 2 030 g, Länge 43 cm. Bei der Aufnahme Temperatur 36°, Allgemeinzustand gut, gute Farbe, schreit kräftig, Unterhautfettgewebe ziemlich gut entwickelt, reichliche Lanugobehaarung, Hoden im Skrotum, innere Organe o. B., Blutbild normal. Während der 1. Woche betrug die Gerinnungszeit bei Prothrombinbestimmungen 10 Minuten. Injektionen von K-Vitamin waren wirkungslos, intramuskuläre Blutinjektionen hatten einen vorübergehenden Effekt. Bei den beiden Geschwistern war die Sachlage dieselbe. Am 4. Tage mässige Gelbfärbung der Haut, die während der 3. Woche ganz verschwand. Keine Zyanoseanfälle, keine nachweisbaren Ödeme. Das Kind wurde während der 1. Woche mit der Sonde gefüttert, trank vom 8. Tage an gut mit dem Sauer, wurde im Alter von 2 Wochen erstmalig an die Brust gelegt und bekam eine Woche später fünfmal die Brust. Es erhielt die ganze Zeit ausschliesslich Frauenmilch, mit Ausnahme der 5 ersten Tage, an denen es wie die Geschwister ausserdem abgekochtes Wasser per os bekam. Das Kind lag schon von Anfang an im Bett. Es wies nie irgendwelche Zeichen von Infektion auf, hatte nie Durchfall. Wie die Geschwister bekam es am 3. und 9. Tage je eine Stossdosis Vitamin D<sub>2</sub> (zusammen 500 000 Einheiten). Hämoglobingehalt des Blutes am 2. Tage 152 %, kurz vor der Entlassung (34. Tag) 116 %. Röntgenuntersuchung der Handknochen (34. Tag) ergab hier wie bei den Geschwistern keine Anzeichen einer Rachitis. Das Kind wurde am 38. Tage in gutem Zustand mit einem Gewicht von 2 560 g und einer Länge von 48 cm entlassen.

Nachuntersuchung im Alter von 6 Monaten: Gewicht 6 500 g, Länge 62,5 cm, keine Anzeichen von Rachitis, Hämoglobin 92 %.

*Drilling 2.* Nr NS 449/44. ♂, Geburtsgewicht 1 850 g, Länge 42,2 cm. Bei der Aufnahme Temperatur 36,1°, Allgemeinzustand gut, schreit kräftig, gute Farbe, Unterhautfett spärlich, reichliche Lanugobehaarung, Hoden im Skrotum, innere Organe o. B. Kein nennenswerter Hautikterus. Blutbild normal, keine Zyanoseanfälle, keine nachweisbaren Ödeme. Das Kind wurde während der 1. Woche mit der Sonde gefüttert, trank in der 2. Woche mit dem Sauer, wurde in der 3. zum ersten Mal an die Brust gelegt und bekam von der 4. an fünfmal die Brust. Dieses Kind erhielt, wie auch Drilling 3, neben der Frauenmilch täglich eine Zulage von 10 ml Aminosol-Glykose (2,5 g Kaseinhydrolysat) pro kg

Körpergewicht. Es lag schon von Anfang an im Bett und konnte von der 4. Woche an die Temperatur ohne Wärmflaschen aufrechterhalten. Es wies während des Krankenhausaufenthalts niemals irgendwelche Anzeichen einer Infektion auf und hatte nie Durchfall. Der Hämoglobingehalt des Blutes betrug am 2. Tage 137 %, am 34. 89 %. Das Kind wurde am 38. Tage in gutem Zustand mit einem Gewicht von 2 820 g und einer Länge von 48 cm entlassen.

Nachuntersuchung im Alter von 6 Monaten: Gewicht 6 500 g, Länge 63,5 cm, keine Anzeichen von Rachitis, Hämoglobin 70 %.

Drilling 3. Nr NS 448/44. ♂, Geburtsgewicht 1 650 g, Länge 42,5 cm. Bei der Aufnahme Temperatur 35,6°, schreit schwach, bewegt sich wenig, Unterhautfett schwach entwickelt, reichliche Lanugobehaarung, Hoden im Skrotum, innere Organe o. B., Blutbild normal. Mässiger Hautikterus, der bald verschwand. Während der ersten Tage des Krankenhausaufenthalts musste dem Kind wegen hochgradiger Zyanose Sauerstoff zugeführt werden, später keine Zyanoseanfälle. Niemals irgendwelche nachweisbaren Ödeme. Das Kind lag schon von Anfang an im Bett, konnte aber erst von der Mitte der 4. Woche an die Temperatur ohne Wärmflaschen aufrechterhalten. Es wurde während der 1. und des grösseren Teils der 2. Woche mit der Sonde ernährt und trank dann mit dem Sauger bis zum Alter von 1 Monat, wo es 5mal täglich an die Brust gelegt wurde. Das Kind konnte äusserer Umstände wegen nicht eher die Brust erhalten. Während der ersten Lebenstage ungleichmässige, fluktuierende Temperatur. Am 10. Tage erkrankte das Kind an einer Infektion der oberen Luftwege, die während des ganzen Krankenhausaufenthalts in mehr oder weniger heftiger Form anhielt. Die Werte der Mikro-SR schwankten von 16 bis zu 25 mm in 1 Stunde. Mit Ausnahme eines schweren Zyanoseanfalls am 47. Tage war der Zustand des Kindes jedoch während der ganzen Zeit verhältnismässig wenig beeinträchtigt, es nahm ausgezeichnet zu, hatte weder Erbrechen noch Durchfälle. Der Infektion wegen lag das Kind länger im Krankenhaus als seine Geschwister und wurde erst am 53. Tage entlassen. Es befand sich da in gutem Zustand und hatte nur noch etwas Schnupfen. Das Gewicht war 3 100 g, die Länge 49,5 cm. Der Hämoglobingehalt des Blutes, der am 2. Tage 112 % betragen hatte, lag nun bei 70 %.

Nachuntersuchung im Alter von 6 Monaten: Gewicht 5 550 g, Länge 61 cm, keine Anzeichen von Rachitis, Hämoglobin 94 %.

Das Versuchsergebnis geht aus Tabelle 1 hervor.

*Drillinggruppe 2.* Eltern gesund, Mutter 20 Jahre alt, Erstgebärende, Schwangerschaftsverlauf normal. Die Kinder wurden reichlich 3 Wochen vor dem berechneten Zeitpunkt geboren (spontane Entbindung), Drilling 1 und 3 in Kopflage, Drilling 2 in Steisslage. Unmittelbar nach dem Partus erhielt jedes Kind 10 mg K-Vitamin; sie waren alle in gutem

Tabelle 1.

Gewichtszunahme während der 5 ersten Lebenswochen bei einer Gruppe Drillinge, von welchen der eine ausschliesslich Frauenmilch, die beiden anderen Frauenmilch + Zusatznahrung von Aminosol-Glykose in einer Dosis von 10 ml (2,5 g Kaseinhydrolysat) pro kg Körpergewicht und Tag erhalten hatten. Drilling 1 und 3 mit grösster Wahrscheinlichkeit eineiig.

Alter	Körpergewicht		
	Drilling 1	Drilling 2	Drilling 3
	Frauenmilch	Frauenmilch + Aminosol-Glykose	
Geburt . . . . .	2 030 g	1 850 g	1 650 g
1 Woche . . . . .	1 900 »	1 800 »	1 620 »
2 Wochen . . . . .	2 030 »	2 020 »	1 980 »
3 » . . . . .	2 230 »	2 260 »	2 130 »
4 » . . . . .	2 300 »	2 440 »	2 320 »
5 » . . . . .	2 460 »	2 680 »	2 500 »
38 Tage . . . . .	2 560 »	2 820 »	2 610 »
Gewichtszunahme an den 38 ersten Tagen	530 g	970 g	960 g

Zustand. Drilling 2 und 3 waren eineiig. Sie wurden einige Stunden nach der Geburt in das Sachs'sche Kinderkrankenhaus verlegt. Aus den dortigen Krankenblättern folgende Einzelheiten:

Drilling 1. Nr S 159/45. ♀, Geburtsgewicht 1790 g, Länge 43 cm. Bei der Aufnahme guter Allgemeinzustand, gute Farbe, guter Tonus und Turgor, schreit kräftig, innere Organe o. B. Prothrombin-index 100. Am 4. Tage leichter Hautikterus, der nach einigen Tagen verschwand. Temperatur während der 6 ersten Tage unregelmässig mit Zacken etwas über 38°. Keine Zyanoseanfälle, keine Ödeme oder Durchfälle. Nie irgendwelche Anzeichen von Infektionen. Vom 6. bis zum 23. Tage bekam dieses Kind, wie auch die Geschwister, insgesamt 500 000 Einheiten Vitamin D<sub>2</sub>. Als Grundnahrung erhielt es, desgleichen die Geschwister, ausschliesslich Frauenmilch, nur während der allerersten Tage ausserdem abgekochtes Wasser per os. Vom 2. Lebenstage an täglich Zulage von Aminosol-Glykose in einer Dosis von 10 ml (2,5 g Kaseinhydrolysat) pro kg Körpergewicht. Der Hämoglobingehalt des Blutes betrug am 1. Tage 136 %, am 26. 100 %.

Drilling 2. Nr S 160/45. ♂, Geburtsgewicht 1960 g, Länge 43 cm. Bei der Aufnahme guter Allgemeinzustand, gute Farbe, guter Tonus und Turgor, Unterhautfett verhältnismässig gut entwickelt, innere Organe o. B., nur ein Hoden im Skrotum. Prothrombinindex 100. Am 5.—6. Tage Andeutung von Hautikterus. Keine Zyanoseanfälle, keine Ödeme, keine Anzeichen von Infektionen, keine Durchfälle. Während der 7 ersten Tage ungleichmässige Temperatur mit Zacken bis 37,5°. Während der 2. und 3. Woche reichliche Hautschuppung. Vom 2. Lebenstage an bekam das Kind täglich unverdautes Kasein in einer Dosis von 2,5 g pro kg Körpergewicht als Zusatznahrung. Der Hämoglobingehalt des Blutes betrug am 1. Tage 136 %, am 26. 117 %.

Drilling 3. Nr S 161/45. ♂, Geburtsgewicht 1900 g, Länge 41,5 cm. Bei der Aufnahme Allgemeinzustand gut, schöne, rosige Farbe, guter Tonus, Turgor o. B., Unterhautfett verhältnismässig gut entwickelt, innere Organe o. B., keine Hoden im Skrotum. Prothrombinindex am 1. Tage 63, am 2. 100. 4.—6. Tag leichter Ikterus. Keine Zyanoseanfälle, keine Ödeme. Nie irgendwelche Anzeichen von Infektionen, keine Durchfälle. Wärmeregulation von Anfang an relativ gut. Vom 2. Tage an täglich Zulage von Kaseinhydrolysat (Aminosol) in einer Dosis von 2,5 g pro kg Körpergewicht. Hämoglobingehalt am 1. Tage 136 %, am 26. 98 %.

Das Versuchsergebnis wird aus Tabelle 2 ersichtlich.

Bei dem in Tabelle 2 wiedergegebenen Ernährungsversuch erhielten die Kinder täglich die gleiche Menge Frauenmilch (aus demselben Behälter) pro kg Körpergewicht. Die zugeführte Proteinmenge (Kasein bzw. Kaseinhydrolysat) war ebenfalls dieselbe (täglich 2,5 g pro kg Körpergewicht). Besonderes Interesse gebührt dem Unterschied des Gewichtsanstiegs zwischen Kind 2 und 3, *die eineiig waren*. Die Kalorienmenge je kg und Tag ist in beiden Fällen gleich gross. Der einzige Unterschied ist der, dass in dem einen Falle Kasein, in dem anderen Kaseinhydrolysat gegeben wurde. Die Gewichtszunahme bei dem Kinde mit Kasein beträgt nur 53 % von derjenigen bei dem Kinde mit Aminosäurengemisch. Drilling 1 empfing infolge des Zuckergehalts in der Aminosol-Glykose täglich ca. 10 Kalorien mehr pro kg Körpergewicht, als die beiden anderen Kinder, und ausserdem einen Extrazuschuss von Salzen. Trotzdem nahm das Kind wenig mehr zu als Drilling 3, der nur Kaseinhydrolysat als Zulage bekommen hatte. Das Resultat dieses Versuchs macht ersichtlich,



Tabelle 2.

Gewichtszunahme während der 28 ersten Tage bei einer Gruppe Drillinge, von welchen einer als Zusatznahrung Aminosol-Glykose, einer unverdautes Kasein und einer schliesslich Kaseinhydrolysat (Aminosol) erhalten hatte. Drilling 2 und 3 waren eineiig.

Alter	Körpergewicht		
	Drilling 1	Drilling 2	Drilling 3
	Frauenmilch + Aminosol- Glykose	Frauenmilch + Kasein	Frauenmilch + Kaseinhydrolysat (Aminosol)
Geburt . . . . .	1 790 g	1 960 g	1 900 g
1 Woche . . . . .	1 790 »	1 840 »	1 860 »
2 Wochen . . . . .	1 950 »	1 850 »	1 980 »
3 » . . . . .	2 080 »	2 000 »	2 190 »
4 » . . . . .	2 290 »	2 210 »	2 370 »
Gewichtszunahme an den 28 ersten Tagen	500 g	250 g	470 g

dass die Zulage von Aminosäuren für die Mehrzunahme ausschlaggebend ist.

In Tabelle 3, 4 und 5 ist das bisher in drei verschiedenen Gewichtgruppen mit dem Aminosäurengemisch behandelte Material zusammengestellt; zum Vergleich dient das Verhalten solcher Kinder, die während des 1. Lebensmonats nur Frauenmilch erhalten hatten. Dieses Vergleichsmaterial besteht aus in den verschiedenen Stockholmer Kinderkrankenhäusern sowie in der Kinderabteilung in Kristianstad<sup>1</sup> während der letzten Jahre behandelten Kindern. Es sei hier bemerkt, dass eine ganze Anzahl dieser Kinder neben Frauenmilch während des letzten Teils des 1. Monats Kasein oder Glykose bzw. beides als Zusatznahrung erhalten hatte. Naturgemäss kann dieses Vergleichsmaterial nicht als in jeder Beziehung befriedigend gelten. Die allgemeine Pflege

<sup>1</sup> Verf. gestattet sich, den betreffenden Herren Chefärzten für die bereitwillige Überlassung der Krankenblätter seinen Dank auszusprechen.

Tabelle 3.

Gewichtszunahme während des 1. Monats bei Frühgeburten mit einem Geburtsgewicht von 1 301—1 400 g.

Alter	Kinder, die nur Frauenmilch erhalten hatten		Kinder, die Frauenmilch + Aminosol-Glykose erhalten hatten	
	Anzahl Fälle	Gewicht, Mittel	Anzahl Fälle	Gewicht, Mittel
Geburt . . . . .	30	1 368 g	7	1 354 g
1 Woche . . . . .	29	1 249 »	7	1 376 »
2 Wochen . . . . .	28	1 354 »	7	1 521 »
3 » . . . . .	23	1 505 »	6	1 697 »
1 Monat . . . . .	21	1 697 »	6	2 008 »
Gewichtszunahme während des ersten Lebensmonats . .		329 g		654 g

Tabelle 4.

Gewichtszunahme während des 1. Monats bei Frühgeburten mit einem Geburtsgewicht von 1 601—1 700 g.

Alter	Kinder, die nur Frauenmilch erhalten hatten		Kinder, die Frauenmilch + Aminosol-Glykose erhalten hatten	
	Anzahl Fälle	Gewicht, Mittel	Anzahl Fälle	Gewicht, Mittel
Geburt . . . . .	30	1 659 g	7	1 668 g
1 Woche . . . . .	24	1 547 »	7	1 650 »
2 Wochen . . . . .	27	1 648 »	7	1 904 »
3 » . . . . .	29	1 756 »	5	2 056 »
1 Monat . . . . .	27	1 939 »	5	2 260 »
Gewichtszunahme während des 1. Lebensmonats . .		280 g		592 g

Tabelle 5.

Gewichtszunahme während des 1. Monats bei Frühgeburten mit einem Geburtsgewicht von 1 901—2 000 g.

Alter	Kinder, die nur Frauenmilch erhalten hatten		Kinder, die Frauenmilch + Aminosol-Glykose erhalten hatten	
	Anzahl Fälle	Gewicht, Mittel	Anzahl Fälle	Gewicht, Mittel
Geburt . . . . .	38	1 961 g	9	1 962 g
1 Woche . . . . .	37	1 813 »	9	1 900 »
2 Wochen . . . . .	38	1 925 »	8	2 079 »
3 » . . . . .	36	2 036 »	6	2 223 »
1 Monat . . . . .	25	2 226 »	6	2 523 »
Gewichtszunahme während des 1. Lebensmonats . .	265 g		561 g	

der Kinder, wie auch die Ernährungstechnik, ist in den einzelnen Krankenhäusern nicht dieselbe. Auch die zugeführten Mengen Frauenmilch schwanken etwas. Zu einem durchaus einwandfreien Material dürfte man nur gelangen können, indem man in derselben Abteilung jedes zweite Kind mit dem Aminosäurengemisch und die übrigen mit Zulagen der entsprechenden Menge unverdauten Kaseins behandelt. Überdies muss die zugeführte Kalorienmenge pro kg Körpergewicht und Tag in der Versuchsgruppe ebensogross sein wie in der Vergleichsgruppe. Eine derartige Untersuchung ist aus praktischen Gründen schwer durchführbar, und das Sammeln eines einigermaßen hinreichenden Materials würde eine unverhältnismässig lange Zeit in Anspruch nehmen. Sehr viel dürfte übrigens selbst durch dieses Vorgehen nicht zu gewinnen sein. Der Mehranstieg des Gewichts ist, bei Beurteilung nach den bisherigen Untersuchungsergebnissen, ein so grosser, dass ein solches Material kaum als erforderlich erachtet werden kann. Ganz anders wäre die Sachlage, wenn es sich lediglich um eine geringe Differenz handeln würde. Das bisher kontinuierlich be-

handelte Material ist nicht gross genug, um eine nähere Analyse zu gestatten. Die Mehrzunahme ist jedoch, wie aus den beigefügten Tabellen erhellt, bei der Behandlung mit Aminosäuren ganz augenfällig.

Untersuchungen über die klinischen Verhältnisse (Wachstum, Rachitis, Anämie, Infektionen, Durchfälle, Blutehemismus usw.) bei regelmässiger Zufuhr von Aminosäuren sind zur Zeit im Gange. Rein physiologisch betrachtet muss diese Behandlung bestimmte Vorteile bieten. Die einstweiligen Erfahrungen sprechen auch in diesem Sinne. Das Material reicht aber zu einer statistischen Bearbeitung noch nicht aus, besonders mit Rücksicht auf die hohe Variabilität, mit der wir in diesem frühen Alter stets zu rechnen haben. Das einzige, was sich vorläufig sagen lässt, ist, dass sich bisher nichts ergeben hat, was dieser Behandlungsform als Nachteil angerechnet werden könnte.

Die Erfahrungen bei dem vorliegenden Material dürften auch eine gewisse Verkürzung der Behandlungsdauer erhoffen lassen. Zur Beantwortung dieser Frage wäre ein Abteilungsmaterial mit Behandlung jedes zweiten Kindes erwünscht. Man kann jedoch durch Vergleich mit den Behandlungszeiten während des unmittelbar vorangehenden Jahres zu einer gewissen Beurteilung gelangen. Eine Vorbedingung dabei ist, dass die Behandlung während der ganzen Zeit einheitlich war. In der Säuglingsabteilung der Allgemeinen Entbindungsanstalt ist diese Voraussetzung erfüllt. Hier sind die Möglichkeiten, die Mütter unterzubringen, auch so gross, dass die Kinder nicht unnötig lange in der Abteilung bleiben müssen, bis für die Mütter Unterkunft geschaffen worden ist. Wenn man die höheren, mehr Kinder enthaltenden Gewichtsgruppen mit Rücksicht auf die Dauer der Pflege in der Abteilung miteinander vergleicht, dann findet man folgendes: Bei 22 in den Jahren 1942/43 gepflegten infektiionsfreien Kindern mit Geburtsgewichten zwischen 2 001 und 2 200 g war die mittlere Dauer des Krankenhausaufenthalts 27 Tage. Bei 20 in den Jahren 1944/45 in der Abteilung betreuten, denselben Bedingungen genügenden Kindern, die aber mit dem Aminosäurengemisch behandelt worden waren, betrug die entsprechende Zeit 18 Tage. Diese Zahlen sind freilich unsicher; erstens einmal

handelt es sich um ein sehr kleines Material, sodann waren ja die Kinder der beiden Gruppen zu verschiedenen Zeiten Insassen der Abteilung gewesen.

### *Erörterung.*

Die Säuglingssterblichkeit in der ersten Lebenszeit ist überall eine hohe und hat sich in gewissem Grade denjenigen Massnahmen gegenüber als refraktär erwiesen, die genügt hatten, um das markante Absinken der Mortalität während des übrigen Teils des ersten Lebensjahres zu bewirken. Der Anteil der nicht ausgehenden Kinder an diesen hohen Sterblichkeitszahlen ist sehr gross (SWANSON, TURNER und ADAIR, ALEXANDER, WALLGREN, YLPPÖ u. a.). Auf diese abnorm hohe Mortalität der Frühgeborenen ist die noch immer so erhebliche Frühsterblichkeit bei den Säuglingen in erster Linie zurückzuführen. Hierdurch wird naturgemäss die Betreuung der Frühgeburten zu einer der wichtigsten Fragen auf dem Gebiet der Sozialpädiatrie. Man hat sich dementsprechend in neuerer Zeit aufs eifrigste bemüht, nicht nur die Zahl der Frühgeburten zu reduzieren, sondern auch den mit mangelhafter Lebensreife geborenen Kindern während der ersten Lebenszeit eine bessere Pflege angedeihen zu lassen.

Was die Ernährung anlangt, so scheint man darüber einig zu sein, dass die Frühgeburt frisch abgepumpte Milch der eigenen Mutter erhalten soll, erst in zweiter Linie frische Frauenmilch anderen Ursprungs, und nur, falls auch dies unmöglich ist, sterilisierte Frauenmilch (von REUSS u. a.). Einer regelmässigen Zufuhr von Kolostrum während der ersten Lebenszeit wird auch grosse Bedeutung beigelegt. Das Kolostrum ist auffallend eiweissreich und, was in Beziehung auf die hier erörterten Fragen wichtig ist, noch reicher an Molkeneiweissstoffen als die fertige Frauenmilch. Ein beträchtlicher Teil dieser art- und bluteigenen Molkenalbumine und -globuline dürfte beim menschlichen Säugling und namentlich beim Neugeborenen die Darmwand passieren, ohne zuvor abgebaut worden zu sein. Dies gilt in noch höherem Grade für die Frühgeburten. Bei diesen haben wir, wenigstens während der ersten Lebenswochen, mit einem unentwickelten, mangelhaft

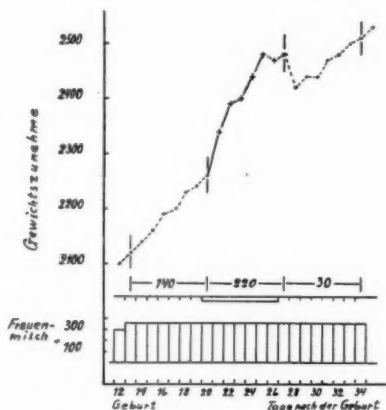


Abb. 5. Gewichtszunahme bei einer Frühgeburt mit menschlichem Plasma als Zusatznahrung. In der Gewichtskurve bezeichnet + + + + + eine Periode mit Plasma und — Plasma in einer Tagesdosis von 2,5 g pro kg Körpergewicht.

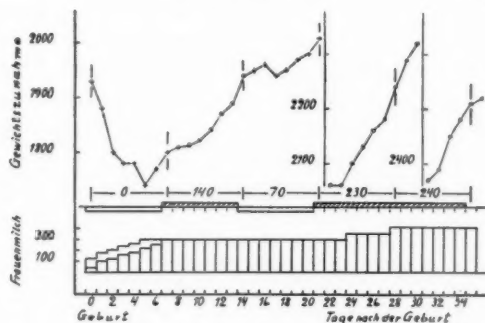


Abb. 6. Kaseinhydrolysat und menschliches Plasma als Zusatznahrung.

funktionierenden Fermentsystem sowie mit einer sehr hohen Permeabilität des Magen-Darmkanals zu rechnen. Die Durchführung einer regelmässigen Ernährung mit Kolostrum bereitet aber nicht selten grosse Schwierigkeiten. Oft ist es an den ersten Tagen schwer, die Milchsekretion bei der Mutter eines vorzeitig geborenen Kindes in Gang zu bekommen, und die anderweitige Beschaffung von Kolostrum pflegt auch nicht leicht zu sein. Man

hat infolgedessen einen anderen Weg eingeschlagen und das Kolostrumeiweiss zu ersetzen versucht. Am nächsten lag dabei die Zufuhr von Blutserum oder -plasma. Es sind auch Versuche nicht nur mit menschlichem, sondern ausserdem mit tierischem Serum angestellt worden, und zwar mit sowohl parenteraler wie peroraler Verabreichung. Zu eindeutigen Ergebnissen ist man nicht immer gelangt.

Ich habe bei einer Fallserie Versuche teils mit menschlichem und teils mit tierischem Serum als Zulage neben der Frauenmilch vorgenommen. Aus praktischen Gründen wurde in der Regel Trockenplasma verwendet, und die Dosierung war dieselbe, wie sie oben für Kaseinhydrolysat angegeben ist (2,5 g pro kg Körpergewicht und Tag). Diese Dosierung führte in der Mehrzahl der Fälle nach der Neugeborenenperiode zu einer auffälligen Mehrzunahme, die jedoch oftmals schon nach wenigen Tagen abgeklungen war. Das vorderhand behandelte Material ist zu klein, und die Zahl der Versuche mit Vergleich zwischen Aminosäuren- und Plasmabehandlung ist zu gering, um eine eingehendere Erörterung der Frage zu gestatten. Die vorstehenden Diagramme (Abb. 5 und 6) veranschaulichen den Sachverhalt bei zwei einzelnen Fällen. Was menschliches Plasma anlangt, so sei erwähnt, dass sich dieses in der Regel nur in begrenzten Mengen beschaffen lässt, und dass die Kosten einer solchen Behandlung diejenigen der Therapie mit Kaseinhydrolysat um ein Vielfaches übersteigen.

### **Zusammenfassung.**

Bei einer Anzahl nicht ausgetragener Kinder, nahezu 150, wurde neben der Frauenmilch ein Aminosäurengemisch, ein enzymatisches Kaseinhydrolysat, als Zusatznahrung entweder periodisch oder kontinuierlich während längerer Zeit gegeben. Das Präparat wurde in der Regel täglich in einer Dosis von 2,5 g Aminosäuren pro kg Körpergewicht zusammen mit einer ebenso grossen Menge Glykose verabreicht.

Die Kinder vertrugen das Aminosäurengemisch in dieser Dosierung gut. Anzeichen von Verdauungsstörungen traten nicht auf.

Die Zufuhr des Aminosäurengemisches in dieser Dosierung hatte bei sämtlichen Fällen eine wesentlich stärkere Gewichtszunahme zur Folge als diejenige, welche bei der Ernährung mit Frauenmilch allein erzielt wurde.

Ein Vergleich zwischen diesem Aminosäurengemisch und einem Gemisch, das unverdautes Kasein, Glykose und Salze in denselben Konzentrationen und Mengenverhältnissen enthielt, ergab in sämtlichen Versuchen einen stärkeren Gewichtsanstieg für die Perioden mit dem Aminosäurengemisch als für die mit Kasein. Durch besondere Experimente, bei denen weder Glykose noch das Salzgemisch zugesetzt worden war, konnte gezeigt werden, dass die Gewichtszunahme von den Aminosäuren verursacht wird.

Die bisherigen Vergleiche scheinen ersichtlich zu machen, dass durch diese Zusatznahrung eine Möglichkeit geschaffen wird, den Krankenhausaufenthalt dieser Kinder abzukürzen.

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## **Occurrence and Significance of Early Periosteal Proliferation in the Diaphyses of Premature Infants.**

By

**NILS MALMBERG.**

In comparison with the attention which has long been paid to the periosteal proliferation in the diaphysis of the long bones, above all of the radius, ulna, fibula, and humerus (WIMBERGER), occurring in advanced rickets after the age of three months, and more particularly in the second half-year of life, little interest has been paid to the form of diaphyseal proliferation of the periosteum which appears at a very early stage in prematurely born infants.

In my studies on the prophylactic treatment of premature infants, begun in 1936 (*Acta Pædiatrica*, Vol. XXIV, 1939, and Vol. XXIX, 1942), I observed and drew attention to these periosteal deposits both with regard to infants which had received prophylactic treatment from the second half of the first week of life and to those which had received no such treatment. In the former category the deposits were present whether the daily dose had been 2 700 or 10 000 international units of vitamin D<sub>3</sub>. In the first-mentioned of the above publications I stated regarding the nature of these periosteal deposits that their connection with rickets does not appear to be definitely established. A reason for the slight uncertainty existing in this respect is the fact that in the series of infants receiving a daily supply of 2 700 international units of D<sub>3</sub> these deposits as well as other clinical and roentgenologic signs of rickets were present, while in another series given doses of 10 000 international units of D<sub>3</sub> some of the infants had periosteal proliferation but even after long observation

periods displayed no roentgenologic or clinical signs of rickets. My investigations have since then been supplemented with a series in which the infants have received one intensive treatment of 500 000 international units of  $D_2$  during the second half of the first week of life.

Periosteal proliferation of the diaphysis as a sign of incipient rickets has been mentioned by several Anglo-Saxon authors, in particular by DAVIDSON & MERRITT, who make the following statement: »Periosteal proliferation has been an early finding, and also an especially prominent one. This manifests itself first as a general thinning and haziness of the lateral margins of the shaft and often can be demonstrated only by reading back from later films, in which the proliferated periosteum is sharply outlined by a heavy deposit of calcium. In our experience this process often accompanies continued activity before antirachitic therapy has been instituted.» But no direct proofs of the connection between rickets and these periosteal abnormalities are furnished.

In 1938, VON CHIARI published a report from the Hamburger Clinic in Vienna on a study of symmetrical periosteal bone changes in the long bones of young infants. In 31 infants, 12 of which had weighed under 2 500 g at birth, the presence of periosteal deposits having no connection with congenital syphilis was demonstrated during the first six months of life. In this connection VON CHIARI strongly — and rightly — criticised the opinion expressed by PÉHU and his collaborators, and also by other investigators, that periosteal proliferation in the early months of life is pathognomonic of congenital syphilis. VON CHIARI, when discussing the possible significance of rickets in the occurrence of these changes pointed out that they were especially well-developed in cases where rickets had been present or had later appeared but stated as his opinion that rickets merely plays the part of a contributory factor. He believed the most likely etiologic factor to be a non-specific inflammatory reaction occurring in connection with pyoderma, which was present in several of his patients. — As there is reason to expect that both rickets and infections can play a part in producing this form of periosteal proliferation VON CHIARI's material can hardly be said to be of use in a discussion on the cause of these

lesions. It will be observed that in his material most of the infants had both rickets and infections of one form or another, such as pyoderma, upper respiratory tract infections, pneumonia, and gastro-enteritis.

My material is composed of 114 premature infants, 72 of which had received prophylactic antirachitic therapy of different intensity as early as the second half of the first week of life. As control subjects were used 42 infants which had not received similar treatment. All the infants were transferred on the first or second day of life from the maternity wards to a special ward for premature infants carefully isolated from infections, where they remained in most cases for 4—6 weeks or for a considerably longer time, according to the birth-weight, after which most of them were sent home and furnished with instructions as to scrupulous protection against infection. The infants were reared for the most part on human milk, supplemented where necessary with small additions of Czerny's flour and butter gruel, during the early part of the investigation, and later with citric acid milk («Citrido»). Besides the clinical examination, roentgen examination of costo-chondral junctions, the bones of the forearm and leg, and in some cases the bones of the upper arm and thigh, was carried out. These examinations were made at intervals of 2—6 weeks in the case of the first series and of 2—4 weeks in the second series, and in the later months of life at intervals of 4—6 weeks. In the third series roentgen examination was undertaken, beginning at 2—3 weeks of age, at 2 week intervals to start with and after 3 months of age at intervals of 4 weeks. The control infants were examined in the same way as the infants in the first and third series. The observation time varied as a rule from 3 to over 12 months; only in a couple of cases was the time as low as  $2-2\frac{1}{2}$  months.

When the roentgenograms thus obtained were studied it was found that a great many of the infants, both treated and non-treated cases, had a linear periosteal deposit of calcium of varying length along the diaphysis, usually on the tibia, but in some cases on the fibula, radius, femur, and humerus. It was generally observed at 4—6 weeks of age, in a few instances at as early as

3 weeks, and in a few cases not until 8—10 weeks of age. In a few infants it was observed at 12 weeks of age. In some it was merely a fine, almost indistinguishable line, in others somewhat thicker. In later films it was possible to distinguish in some instances deposits arranged in layers. (See figs. 1 and 2.) Within 2—4 weeks the deposit in its less severe form had in some instances fused with the bone and become wholly or almost indistinguishable. In cases where the deposit was thicker or in layers it was visible for a long period of time in the form of a thickening of the corticalis. It was sometimes observed that the calcareous deposit was separated from the original cortex by a narrow rarefied zone resembling an extra marrow hole. However, when the films were carefully studied in a good light it was seen in many cases that in the films taken 2—4 weeks before the appearance of the calcium deposit the corticalis was unclear and indistinctly outlined against the soft tissues at the site of the deposit which was later to appear; the surface seemed to be slightly fluffy, and not as in normal bone sharply outlined, indicating that periosteal proliferation of what was probably osteoid tissue which was later to become calcified was in progress, an interpretation which will be discussed later in this paper.

A Wassermann test was carried out in some of the infants after the age of 1 month, as well as on their mothers. The results were consistently negative. It can also be mentioned here that congenital syphilis was extremely rare in Stockholm during the years 1936—1943, the period during which this investigation was in progress, and syphilis can therefore be ruled out as a possible cause of the changes.

It will be seen from table 1 that early signs of a periosteal reaction in the diaphysis of various bones were observed in 27 of the 42 control infants while in 15 there were no such changes. The table also shows that roentgenologic evidence of rickets appeared in a little over half of the total number, or 24 infants, during the observation period; in the majority of these infants, 15 out of 24, periosteal proliferation had previously been established. Rickets subsequently developed, however, in 9 infants in which no periosteal reaction had been demonstrated. A feature of parti-

Table 1.

Control infants receiving no prophylactic treatment: 42.

Birth weight (g)	No periosteal proliferation: 15		Periosteal proliferation: 27	
	No subsequent signs of rickets	Subsequent signs of rickets	No subsequent signs of rickets	Subsequent signs of rickets
1 001—1 500	—	—	—	5
1 501—2 000	4	5	7	7
2 001—2 500	2	4	5	3
Total	6	9	12	15

Table 2.

Series 1. Infants receiving prophylactic treatment: 29. Daily dose of vitamin D<sub>3</sub>, 2 700 international units from and including the 4th—6th day of life.

Birth weight (g)	No periosteal proliferation: 19		Periosteal proliferation: 10	
	No subsequent signs of rickets	Subsequent signs of rickets	No subsequent signs of rickets	Subsequent signs of rickets
1 001—1 500	—	1	4 <sup>1</sup>	3 <sup>1</sup>
1 501—2 000	5	8	2	1 <sup>1</sup>
2 001—2 500	5	—	—	—
Total	10	9	6	4

<sup>1</sup> One infant in each group received 5 400 international units of D<sub>3</sub> per day from and including the 4th day of life.

cular interest was that of the infants in the lowest weight group, viz. those with a birth-weight of 1 001—1 500 g, which are known to have the greatest tendency to develop rickets, all 5 of them displayed both periosteal abnormalities and subsequent evidence of rickets.

As regards the 72 infants treated prophylactically, they all received the treatment early, beginning in the first week of life, but the intensiveness of the treatment was different for different categories, as may be seen from tables 2—4. Twenty-six infants

Table 3.

Series 2. Infants receiving prophylactic treatment: 29. Daily dose of vitamin D<sub>3</sub>, 10 000 international units from and including the 4th—7th day of life.

Birth weight (g)	No periosteal proliferation: 15		Periosteal proliferation: 14	
	No subsequent signs of rickets	Subsequent signs of rickets	No subsequent signs of rickets	Subsequent signs of rickets
1 001—1 500	—	—	5	1
1 501—2 000	15	—	7	1
2 001—2 500	—	—	—	—
Total	15	—	12	2

Table 4.

Series 3. Infants receiving prophylactic treatment: 14. Intensive treatment, 500 000 international units of vitamin D<sub>2</sub> in 2 doses, on the 4th—7th day of life.

Birth weight (g)	No periosteal proliferation: 11		Periosteal proliferation: 3	
	No subsequent signs of rickets	Subsequent signs of rickets	No subsequent signs of rickets	Subsequent signs of rickets
1 001—1 500	5	—	—	—
1 501—2 000	6	—	2	1?
2 001—2 500	—	—	—	—
Total	11	—	2	1?

in the first series received a daily dose of 2 700 international units of D<sub>3</sub> and 3 received 5 400 international units of D<sub>3</sub> in periods of 4—6 weeks with 2 week pauses. In the second series, 10 000 international units of D<sub>3</sub> were supplied daily in the same way to 29 infants. During the first week of treatment, the daily supply of vitamin D was in both these series slightly less than the amount stated above, as the infants were given gradually increasing doses in order to lessen the likelihood of digestive disturbances. In the third series 500 000 international units of D<sub>2</sub>

were given in one short intensive treatment period to 14 infants. As may be seen from tables 2—4, and as I pointed out in my paper of 1939, mentioned earlier, a dosage of 2 700 or 5 400 international units of vitamin D<sub>3</sub>, instituted in the first week of life, does not constitute an adequate protection against rickets. With a dosage of 10 000 international units of D<sub>3</sub>, starting at the same age, practically all infants can be protected from even the slightest roentgenologic traces of rickets. The infant in the 1 001—1 500 g weight group which, according to table 3, developed rickets had a birth-weight of only 1 000 g. Both this infant and the child mentioned in the following weight group had only very slight traces of the disease. In the series of infants treated by one short intensive treatment there was one which *possibly* displayed minimal roentgenologic signs of rickets, though this was very doubtful.

With regard to the question of interest in the present paper, concerning the development of periosteal proliferation in diaphyses, it can be read from tables 2—4 that with the most intensive form of prophylactic treatment the number of cases displaying this reaction in the periosteum can be greatly reduced but not wholly eliminated. In my opinion, it is particularly noteworthy that all 5 infants in the 1 001—1 500 g weight group escaped both periosteal changes and later evidence of rickets (see table 4), whereas in all the control infants in the same weight group (table 1) and in 13 out of 14 infants (tables 2 and 3) receiving continuous vitamin D therapy these deposits of calcium were present in the periosteum. When at the same time it is known that it is precisely these infants born long before term which are especially pre-disposed to rickets, and that in this particular category of infant both periosteal changes and the usual, subsequent rachitic signs fail to appear when an intensive course of vitamin D is applied in the first week of life, it would seem logical to assume that this incipient periosteal proliferation in the diaphysis of long bones is one of the earliest observable signs of rickets. The fact that in a large number of cases roentgenologic signs of rickets appear at costo-chondral junctions or in wrist and ankle joints 4—6 weeks after a proliferated periosteum has been observed is further evidence in the same direction. In ex-

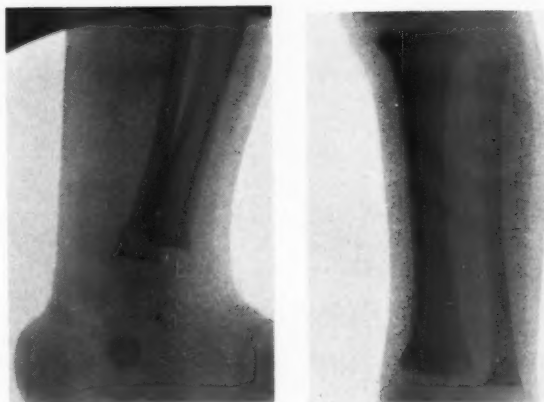


Fig. 1. A boy, birth weight 1 000 g. At 6 weeks of age periosteal proliferation in the tibia and fibula. (In the ulna also.) The metaphyses display fraying of the type seen in rickets.

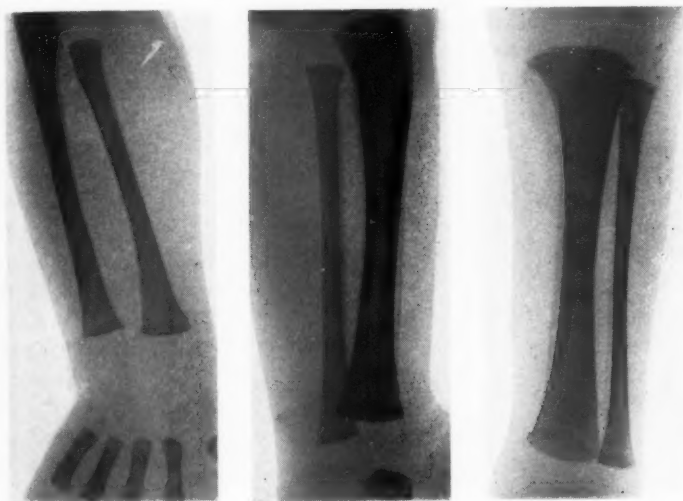


Fig. 2. A boy, birth weight 1 380 g.

- a) At age of 4 weeks. Fresh periosteal proliferation in tibia, fibula, and ulna. No roentgenologic signs of rickets at costo-chondral junctions, or wrist and ankle joints.





b) At age of 8 weeks. The thickness of the periosteal deposits has increased. There is now a clearly distinguishable deposit in the radius also. Traces of rickets at the costo-chondral junctions. In the ulna the surface of the metaphysis has become slightly concave, and in the tibia there is an osteophytic outgrowth at the metaphysis.



c) At age of 12 weeks. The periosteal deposits are now fused with the diaphyses.

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planation of why these pathologic changes tend to arise particularly in long bones, most frequently in the tibia, WIMBERGER and ELIOT have suggested a mechanical factor due to muscle action.

Proliferation of the periosteum seems to occur in certain non-treated infants without subsequent appearance of rachitic signs. This feature is evident from table 1 (12 out of 42 infants). The question of whether the changes in these cases are to be regarded as a reflection of vitamin D deficiency or not cannot be decided from our present knowledge on the subject. But this explanation is not an impossible one.

The periosteal abnormalities described in this paper which have been observed in infants as young as 4—6 weeks, and which, since they show calcification even at this early stage must have been in existence for some time, possibly several weeks, constitute further evidence in support of my previously advanced view, that premature infants, especially the most underdeveloped ones, should be given intensive antirachitic therapy as early as possible, starting from about the first week of life, in order to ensure the greatest possible measure of protection from even the mildest forms of rickets.

### Summary.

The majority of prematurely born infants show at an early age, 4—6 weeks, at a stage when there are no signs of rickets at the epiphysis, a greater or lesser degree of periosteal proliferation at the diaphysis of the long bones, especially of the tibia. Reasons are advanced to support the view that this pathologic feature is a sign of vitamin D deficiency and is to be regarded as the earliest roentgenologic evidence of rickets, often appearing 4—6 weeks before the epiphyseal changes.

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FROM THE PEDIATRIC CLINIC OF KAROLINSKA INSTITUTET AT KRON-  
PRINSESSAN LOVISA'S CHILDREN'S HOSPITAL, STOCKHOLM.  
HEAD: PROFESSOR A. LICHTENSTEIN.

## **Patent Ductus Arteriosus.**

### **Diagnosis and Indications for Operation.**

By

**EDGAR MANNHEIMER, M. D.**

The first successful operation for patent ductus arteriosus was done in 1938 by the American surgeon Gross. By ligating the vessel, he forced the circulation back into normal paths. This was the first time that causal therapy was used for a congenital heart defect.

MAUD ABBOTT, the great pioneer in this field, was present shortly before her death at a meeting where Gross described his operation. She said then: »He has revolutionized the outlook on the therapeutic aspects of congenital heart disease. Of course, the patent ductus does seem the most get-at-able anomaly for surgical intervention, but we have not ended there and it is a great event in this field.»

The first operation in Europe was done by CRAFOORD at Sabbatsbergs hospital, Stockholm, on May 30th 1941 and until April 1945 he has operated on 38 cases. In 25 cases the patients were under 15 years of age and 22 of them were children from the pediatric clinic of Kronprinsessan Lovisa's Childrens Hospital. There are two deaths. The one was a girl of four, who got heart collapse at the end of the operation. The other case was an adult patient with endocarditis in her ductus. She got a recurrence and died after a second operation. All other cases have cured and no recurrence is seen among them.

CRAFOORD, MANNHEIMER and WIKLUND have published a paper on diagnostics and operation technique in *Acta Chirurgica Scandinavica* Vol. XCI 1944—45. Here I only want to give a brief general survey.

*The diagnosis patent ductus arteriosus is nearly only based upon the continuous murmur.*

In 1900 GIBSON lectured on patency of the ductus arteriosus and its diagnosis to the students in Edinburgh. He then formulated the concept continuous murmur, which differs from both the systolic and the diastolic murmur in the following respects. It begins in about the middle of systole, is marked by a strong crescendo up to the second heart sound, which is often accentuated, and then declines in strength to die away far forward in diastole. The continuous murmur cannot be due to the heart, for it does not coincide with either systole or diastole. It was this fact which led GIBSON to assume that it was of vascular origin. Lately, it has been verified from different sources that the diagnosis of a patent ductus arteriosus rests almost entirely on the character of the murmur. The other signs and symptoms of the condition may be characteristic enough, but they are of secondary importance to the diagnosis in the individual case. GIBSON's discovery was published in the *Edinburgh Medical Journal* but was soon forgotten. The result was that the continuous murmur remained a fairly unknown concept, seldom mentioned even in cardiologic literature. In later years it is only to be found in the Anglo-Saxon literature (ABBOTT, WHITE).

Fig. 1 shows four cases of patent ductus Botalli before and after operation. The registration is made by means of calibrated phonocardiography (MANNHEIMER, *Acta Pædiatrica*, vol. 28, suppl. 2, 1940). The microphone is placed on the pulmonary orifice where the murmur always has its maximal intensity.

The continuous murmur can also be found in other arterio-venous communications e. g. aneurysms, »venous hum in the neck» and sometimes in cases of persistent truncus communis. In these cases the murmur never has its punctum maximum on the pulmonary orifice.

One question is whether a patent ductus arteriosus may be

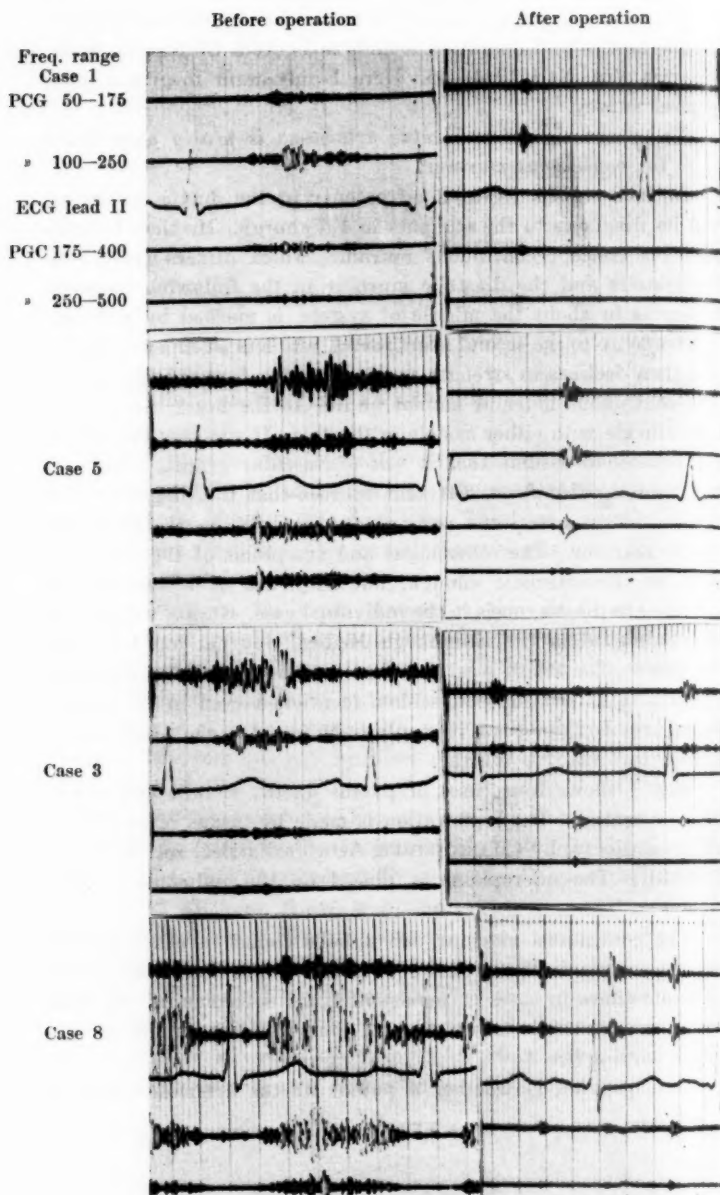


Fig. 1.

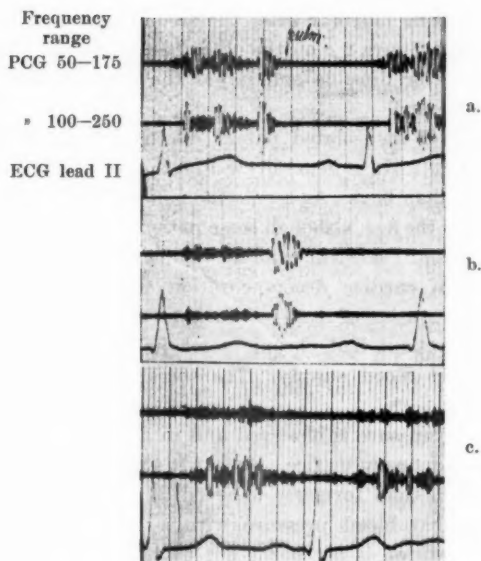


Fig. 2.

- a. Systolic murmur in a case of ventricular septal defect.
- b. Systolic and protodiastolic murmur in a case of luetic regurgitation of the aortic valve.
- c. Continuous murmur.

present without a continuous murmur. ABBOTT said that infants and young children with this disease could show purely systolic murmurs. The heart frequency is so high at that age, that it is questionable whether the continuous murmur can really be recognized on auscultation. There are no phonocardiographic investigations to prove her statement.

For the purpose of differential diagnosis, I have assembled in figure 2 one case of septal defect with a systolic murmur (fig. 2 a), one case of syphilitic insufficiency of the aorta with systolic and protodiastolic murmurs (fig. 2 b) and the continuous murmur in case 8 (fig. 2 c). The systolic murmur in both figure 2 a and 2 b shows vibrations directly after the first heart sound and ends with a distinctly independent second sound. In figure 2 b one

sees the protodiastolic murmur after the second sound. The continuous murmur in figure 2 c on the other hand does not coincide with either systole or diastole and it has the characteristic properties just mentioned.

The *diagnosis* of an isolated patent ductus arteriosus is not particularly difficult. It is generally a question of children, girls much more often than boys. As a rule the general bodily development is normal for the age, although some patients show a moderate degree of infantilism. Transient cyanosis occurs only exceptionally, but other signs of cardiac decompensation are not infrequent. Most often they consist of ease of fatigue and mild dyspnea. One 28-year-old patient had chronic sores in her legs, pointing to poor peripheral blood supply. The sores disappeared after operation.

In some cases *vousure* is observed and in all cases a powerful thrill over the pulmonary orifice. Gerhardt's dulness may occur, but is less common than formerly believed.

The opinion that blood pressure with a large amplitude is typical of the condition is not borne out by my cases. A normal circulating time and normal venous pressure belong to the picture.

Roentgen examination generally shows enlargement of the left side of the heart, a suggested moderate bulging of the pulmonary arch and increased central vascular markings, indicating venous stasis. These roentgenologic signs are not a sure indication of patent ductus arteriosus, for they occur in many cases of heart disease, especially in those of congenital heart defect. Occasionally the roentgen picture is normal.

A normal electrocardiogram is typical of the disease, indicating that the defect lies outside the heart. The secondary changes observed consist of moderate preponderance of either the right or the left side, and slight signs of secondary myocardiac lesion.

The most important observation and that which leads to the diagnosis is the continuous murmur. Its characteristic position in the pulse period and its great intensity can often be ascertained with the stethoscope alone, but phonocardiographic examination is undoubtedly of great help to the diagnosis. As said above the continuous murmur occurs in other conditions than patent ductus

arteriosus. Thus it is not a pathognomonic sign in itself. But there is no other heart defect with a continuous murmur with its maximum over the pulmonary orifice. Therein lies the key to the diagnosis, which is further confirmed by a normal electrocardiogram and typical roentgen changes.

A question of greatest importance is *what cases of patent ductus arteriosus should be operated upon?* One can either operate on the patients who show signs of latent or manifest cardiac decompensation or on all pure cases of the condition. I believe that the second alternative is the right one for the following reasons.

In the first place, different investigations (ABBOTT, BULLOCK, JONES and DOLLEY) show a much shorter life span for persons with a patent ductus arteriosus than for healthy persons. This is also indicated by the fact that the great majority of patients with this condition are children. Adult cases are rare. In the second place, ABBOTT showed that a patent ductus arteriosus involves a great risk of endocarditis in the vessel. No less than 28 of ABBOTT's 92 patients died from this complication. In the third place, the studies of EPPINGER, BURWELL and GROSS show that a patent ductus arteriosus puts a great strain on the heart and that in many cases there is an unsatisfactory supply of blood to the periphery of the body.

In the fourth place, there are social indications for the operation. Because of the powerful continuous murmur these patients are always refused certificates of health and their opportunities of making a living are greatly curtailed. The following case is an example. The patient, an 18-year-old girl, was refused a permanent position at the postoffice in Stockholm because of her heart-defect, which gave her no trouble at all. After operation she was again examined by the post-office physician and is now allowed to apply for a position.

It is altogether too early to make any statement on the effects of the operation, despite the fact that many patients became free of trouble afterward, and some cases with a pathologic roentgen picture before the operation now show normal roentgenograms. Only many years of postoperative observation will tell whether the positive attitude now taken toward the operation is justified to the full.



### Summary.

A short general survey is given on diagnosis and indications for operation in patent ductus Botalli. Until now Crafoord has operated on 38 cases with good results (2 deaths, one of them was a case of endocarditis in her ductus). The symptom which gives the diagnosis is the continuous murmur with its maximal intensity over the pulmonary orifice. The author has the opinion that all cases of isolated patent ductus arteriosus should be operated upon. In cases where the condition is combined with other malformations every case should be judged individually.

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## On the Relationship between Prothrombin Time and Haematocrit Value.

By

GUNNEL MELIN.

QUICK's method for prothrombin time determination is principally performed in the following way. Certain quantities of calcium and thrombokinase (tissue extract) are added to oxalate plasma and the time elapsing till the coagulation of the plasma is measured and constitutes the so-called prothrombin time. Provided that the examined fibrinogen content of the blood does not deviate considerably from the normal, only the prothrombin content in this determination is a variable factor. This is evident from the classical scheme presented below, according to which the coagulation of the blood takes place in two stages.

1. Prothrombin + thrombokinase + calcium = thrombin.
2. Thrombin + fibrinogen = fibrin.

In Sweden, QUICK's method is employed chiefly in a modified form. As a rule, either FIECHTER's or LEHMANN's modification is adopted. In the latter event, citrate is used instead of oxalate with the same quantitative conditions as at the determination of the sedimentation rate. It is therefore possible, if desired, to use ordinary sedimentation rate blood for the determination. — The determination is carried out on whole-blood and but a small blood quantity may suffice in both methods, i. a. only 0.15 and 0.10 ml of blood, respectively. This must be regarded as a distinct improvement of QUICK's method, where venous blood is required. —

<sup>1</sup> Material has also been contributed from the Gynecological and Obstetrical Clinic of Karolinska Sjukhuset and The Epidemic Hospital, Stockholm.

By the introduction of micro-methods, to a far greater extent than formerly, determinations have been possible on infant blood. This kind of investigation has here been attributed great importance owing to the fact that bleedings due to a deficiency in prothrombin constitute one of the most noteworthy affections of the newborn period.

At first, QUICK's method of determining the prothrombin time on plasma was more frequently employed. A few determinations were also performed on diluted plasma. Thus, the plasma of the patient was diluted with plasma in which the prothrombin had been inactivated in various ways. In 1939, KARK and LOSZNER demonstrated that, in patients with a prolongation of the prothrombin time owing to a deficiency in K-vitamins, a dilution of the patient plasma gave a pronounced protraction of the prothrombin times. This protraction is most conspicuous in the larger dilutions. The prolonged time obtained in dilutions in the plasma of healthy persons was but insignificant. SCOZ, BERGAMI, and collaborators, as well as CAMPBELL, and collaborators, have shown that, in cases with merely a small deviation from the normal a prolonged prothrombin time could only be produced in the dilutions. These conditions have also been studied by BLOM who reported similar experiences in 1942.

BLOM's investigation is, however, criticised by LEHMANN, who contends that at a plasma dilution of the kind mentioned above also the relationship between the oxalate and the calcium is changed which, in turn, involves a change in the coagulation times which are no longer comparable to those of the undiluted plasma. The desired effect can be achieved by diluting instead the kinase solution.

Thus, the significance of plasma dilutions of the above-mentioned kind has not been fully elucidated. Nevertheless, it appears probable that a prothrombin dilution may *per se* cause prolonged times. KARK and LOSZNER's observation, for instance, favours this assumption, viz. that a considerably more pronounced prolongation occurred at dilutions of blood derived from individuals with a deficiency of K-vitamins than from healthy persons.

The prothrombin occurs in the plasma and not in the cells of the blood. Accordingly, at prothrombin determination on whole-blood, as in the case of FIECHTER's and LEHMANN's methods, in actual fact a kind of plasma dilution will be dealt with. Thus, the total cellular volume may be expected to play a certain part with regard to the prothrombin time reading. A longer prothrombin time may, possibly, occur in whole-blood than in only plasma. In addition, changes of the prothrombin times should be obtained even at a fixed quantity at variations in the haematocrit values. High haematocrit values (i. e. large volume of red blood corpuscles) involves, as a matter of course, a small volume of plasma in the sample. High haematocrit values should also cause a distinct prolongation of the prothrombin time.

The present author has studied the condition of prothrombin time at plasma dilutions with blood corpuscles in a series of examinations.

#### *Method.*

9 ml of venous blood is deposited in an ordinary record syringe which contains, at the time of the test, 1 ml of M/10 Na-oxalate. A small portion of the oxalate blood is taken away and the rest is centrifuged for 5 minutes. The plasma is then removed by means of a pipette and the remaining pulp of blood corpuscles is divided into 4—5 portions. By mixing different amounts of blood corpuscle pulp and plasma, a dilution series of pulp-plasma is obtained where the two extreme samples consist of pulp and plasma, respectively. However, the pulp sample will also contain some plasma. The haematocrit values of the several solutions are determined with VAN ALLEN's haematocrit (double determinations), according to which the values are reduced with regard to the dilution of the blood with oxalate. The prothrombin time is determined by means of FIECHTER's micro-method. A pan, especially constructed by BROMAN (see Fig. 1) has been used for these determinations. This pan simplifies the examination to a great extent by constituting a water-bath for the tissue extract and the calcium-chloride, as well as for three blood samples. This water-bath has another great advantage, viz. the samples



Fig. 1. An illustration of the pan for the determination of the prothrombin time, as constructed by BROMAN. The lamp in the background serves to illumine the test-tubes from below. The long test-tubes contain tissue extracts and calcium chloride (cp. right hand), the short ones contain the blood sample (cp. left hand).

can be kept down in it during the whole examination and the temperature of the water-bath may, by means of thermostatic regulation, be kept constant.

Five determinations have been made for each dilution and the mean figure of the five values corresponds to the figures used for the drawing of the diagram. Generally, one or two seconds have marked the difference between the shortest time reading and the longest one in the same dilution.

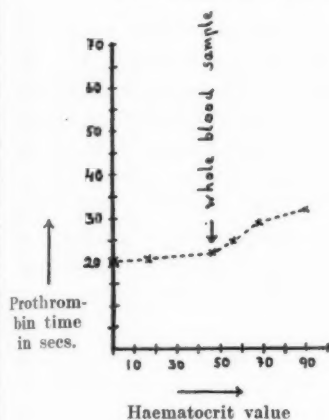


Fig. 2.

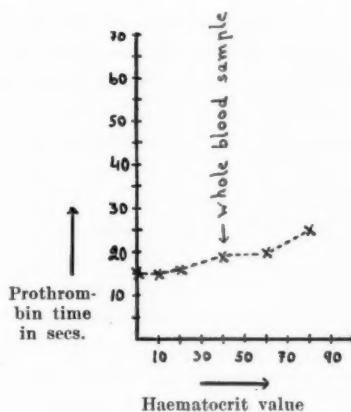


Fig. 3.

Table I.

Haematocrit value . . .	0	17	<b>46</b>	56	68	90	
FIECHTER in secs. . .	20	21	22	25	28	32	Case 1
Haemat. v. . . . .	0	10	20	<b>40</b>	60	80	
FIECHTER . . . . .	15	15	16	19	20	25	Case 2
Haemat. v. . . . .	0	11	24	<b>46</b>	50	60	80
FIECHTER . . . . .	15	17	18	18	20	22	26
							Case 3
Haemat. v. . . . .	3	20	36	<b>45</b>	56	62	70
FIECHTER . . . . .	21	23	24	24	25	27	30
							Case 4
Haemat. v. . . . .	0	12	28	<b>49</b>	55	68	84
FIECHTER . . . . .	17	17	18	20	22	24	26
							Case 5
Haemat. v. . . . .	0	12	25	<b>48</b>	56	64	85
FIECHTER . . . . .	14	14	15	17	18	21	28
							Case 6
Haemat. v. . . . .	0	15	23	<b>55</b>	64	76	
FIECHTER . . . . .	15	15	16	17	20	23	
							Case 7
Haemat. v. . . . .	0	12	22	<b>40</b>	46	57	77
FIECHTER . . . . .	17	17	18	19	21	23	27
							Case 8
Haemat. v. . . . .	0	11	19	<b>48</b>	54	69	92
FIECHTER . . . . .	12	13	13	14	16	17	25
							Case 9
Haemat. v. . . . .	0	14	26	<b>49</b>	58	66	78
FIECHTER . . . . .	16	16	16	18	20	22	25
							Case 10

Determinations on the blood of healthy persons have been made in 10 instances. Five of these cases were adults, the rest being children, who had been admitted to the hospital for mental analysis and did not suffer from any physical troubles. All these cases revealed a comparatively slight, although distinct, prolongation of the prothrombin time at increasing haematocrit values, i. e. increased plasma dilution. This is illustrated in Figures 2 and 3. A marked prolongation of the prothrombin time was only obtained at very high haematocrit values. All the other normal cases show very similar conditions to those in Figures 2 and 3, as will be seen in Table I.

However, quite another aspect is met with in patients, who for some reason or other, have a reduced prothrombin content in the blood. This is exemplified by the following 10 cases.

*Case 11.* E. H.<sup>1</sup> 4546/1943, fem., 29 years. Diagnosis: Acute Hepatitis. Apart from bilateral pleuritis + pericarditis in 1933, and erysipelas in 1942, she has been in good health. At the end of Nov. 1943 tired, and in the beginning of Dec. unwell, tired. 14/12 icterus was ascertained. Admitted to the Epidemic Hospital, 16/12. Meulengracht was then 1/70, fell during the course of two weeks to 1/11. S.R. 16/12: 20 mm/hour, 28/12: 42 mm/hour. Test for prothrombin examination taken 17/12. See Fig. 4.

*Case 12.* E. H. 4532/1943, male, 22 years. Diagnosis: Acute Hepatitis. Severe abdominal tbc as a child, otherwise healthy. Fell ill 3/11 with nausea, 10/11 icterus. After treatment at home for approx. one month to hospital owing to persistent, marked icterus. Meulengracht 7/12: 1/280, fell during the course of 5 weeks to 1/24. S.R. — at admission 2 mm/hour, at discharge 13 mm/hour. Test for prothrombin examination taken 21/12 (Meul. 1/175). See Fig. 5.

*Case 13.* E. H. 146/1943, fem., 20 years. Diagnosis: Acute Hepatitis. Earlier in good health. 10/1 headache, temperature 39.2. 14/1 afebrile. Icterus on the same day. Meulengracht 1/17. 21/1: Meul. 1/24, 4/2: 1/10. S.R. 14/1: 35 mm/hour. 4/2: 22 mm/hour. Test for prothrombin examination taken 21/1.

*Case 14.* E. H. 4717/1943, male, 7 years. Diagnosis: Acute Hepatitis. Earlier in good health. Low condition, lack of appetite at the beginning of Nov. 17/11 icterus, increasing. Admitted to the Epidemic

<sup>1</sup> E. H. = Epidemic Hospital.

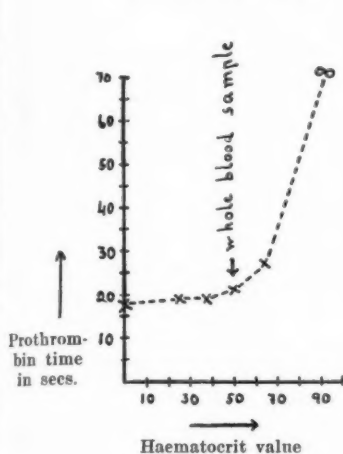


Fig. 4.

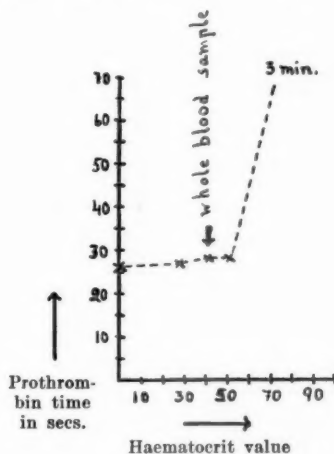


Fig. 5.

Hospital 27/12. Meulengracht 28/12 1/110. 31/1: 1/17. S.R. 8/12: 85 mm/hour. 31/1 33 mm/hour. Test for prothrombin examination taken 30/12. K vitamin. 1 amp. per day for three days, then renews prothrombin time determination. See Fig. 6.

*Case 15.* K. S.<sup>2</sup> Obst. 1996/1943, fem., 29 years. Diagnosis: Embolia pulm + pelvic thrombosis after normal delivery. Earlier in good health. Administered 0.5 + 0.125 grammes A. P. (named anti-prothrombin, metylendihydroxikumarin) a couple of days before the test.

*Case 16.* K.S. Obst. 2233/1943, fem., 30 years. Diagnosis: Primary weak pains. Thrombosis in both legs after parturition 1938. Otherwise earlier in good health. For the sake of prophylaxis 0.25 + 0.25 grammes A. P. were administered a couple of days before the test for the determination of the prothrombin time.

*Case 17.* K. S. Gyn. 2709/1943, fem., 64 years. Diagnosis: Granulosa cell tumour. Op. Prophylactic administration of 0.125 grammes A. P. 3 days in succession, a few days before the determination of the prothrombin time.

*Case 18.* K. L. H.<sup>3</sup> 812/1943, fem., 7 years. Diagnosis: Mb, Werlhof. Healthy before. Tired, lack of appetite, tendency to nose bleeding from

<sup>2</sup> K. S. = Gynecol. and Obstetr. Clin. of Karolinska Sjukhuset.

<sup>3</sup> K. L. H. = Pediatr. Clin. of Kronprinsessan Lovisa's Children's Hospital.



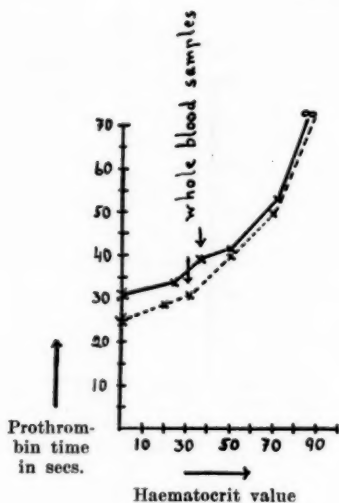


Fig. 6.

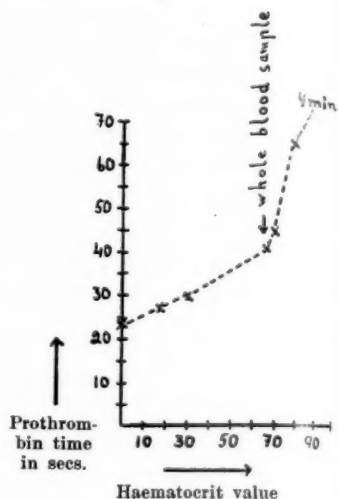


Fig. 7.

the beginning of June 1941. Anemia ever since. In June 1943 an enlargement of the liver and the spleen was observed. Was admitted to hospital 9/10 1943. All the examination results, including the bone medulla punctate, indicated the occurrence of Mb. Werlhof. Fiechter at admission 45, fell to 35 and after K vitamin supply to 25.

*Case 19.* K. L. H. 179/1944, male, 3 days old. Weight at birth: 3 100 grammes. Diagnosis: Myelo-meningocele + pes varus. Parturition without remark. Not given K-vitamin. See Fig. 7.

*Case 20.* K. L. H. 211/1944, male, 6 days old. Weight at birth: 3 880 grammes. Diagnosis: Myelo-meningocele. Parturition without remark. Not given K.vitamin. See Fig. 7.

Since a test cannot be performed on newborns without sinus puncture, and owing to the fact that this intervention has not been considered advisable on children other than those unfit for life, blood from newborns has only been obtainable in 2 cases (cases 19 and 20).

Table II.

Haematocrit value . . . . .	0	25	39	<b>50</b>	64	92	
FIECHTER in secs. . . . .	17	19	19	21	<b>27</b>	$\infty$	Case 11
Haemat. v. . . . .	0	29	<b>41</b>	<b>52</b>	72	82	
FIECHTER . . . . .	<b>26</b>	27	28	28	180	$\infty$	Case 12
Haemat. v. . . . .	0	37	<b>46</b>	<b>62</b>	72	84	
FIECHTER . . . . .	21	24	25	29	35	46	Case 13
Haemat. v. . . . .	0	23	<b>36</b>	50	71	85	Case 14
FIECHTER . . . . .	<b>31</b>	34	39	41	53	$\infty$	before K-vimin
Haemat. v. . . . .	0	20	<b>32</b>	51	70	83	Case 14
FIECHTER . . . . .	25	29	31	40	50	$\infty$	after K-vimin
Haemat. v. . . . .	0	22	<b>40</b>	48	70	82	
FIECHTER . . . . .	30	34	37	42	54	$\infty$	Case 15
Haemat. v. . . . .	0	18	38	<b>46</b>	54	60	80
FIECHTER . . . . .	30	32	35	38	44	54	64
Haemat. v. . . . .	0	27	<b>40</b>	49	54	60	72
FIECHTER . . . . .	26	32	40	48	52	60	74
Haemat. v. . . . .	0	24	<b>32</b>	50	64	80	
FIECHTER . . . . .	29	33	35	44	60	240	Case 18
Haemat. v. . . . .	0	20	32	<b>58</b>	70	83	
FIECHTER . . . . .	19	20	22	25	32	55	Case 19
Haemat. v. . . . .	0	18	30	66	70	80	85
FIECHTER . . . . .	24	27	30	41	45	65	240
							Case 20

*Discussion.*

The examination result will show that a dilution of plasma, containing prothrombin, with the blood corpuscles of healthy individuals affects the prothrombin time but slightly. A marked prolongation of this time is produced only by such a large addition of blood corpuscles as to cause the haematocrit value to approximate to 90. However, when the prothrombin content is, for some reason or other, reduced, e.g., at an injury to the liver after hepatitis, after A. P. treatment, or physiologically during the new born period, such a dilution with blood corpuscles will give rise to considerably prolonged times. The difference between 45 and 70 in the haematocrit values has, as a rule, offered a difference

in time of 15—20 seconds, the difference being  $2\frac{1}{2}$  minutes in one instance.

The author's examination may be criticized in so far the particular method employed causes a change in the oxalate quantity in the samples where plasma has been added or removed by pipette. The relationship oxalate-calcium is, consequently, changed and may, as propounded by Lehmann, give rise to a prolongation of the prothrombin time.

Nevertheless, this source of error cannot play a decisive part with regard to the result of the examination. Thus, it cannot in any way explain the difference in the prolongation of the prothrombin time at increasing haematocrit values as between healthy and »prothrombin-deficient» individuals. It may, conceivably, be the origin of the prolongation which occurs in healthy persons at increasing haematocrit values.

It may be maintained that possible variations in the total volume of red blood corpuscles will affect the prothrombin time to a marked extent in conditions involving a comparative deficiency of prothrombin. Accordingly, in all cases with a prolonged prothrombin time the total volume of red blood corpuscles will quit an important part with regard to the time reading. Patients with varying total volumes of red blood corpuscles will not, of course, have directly comparable values of the prothrombin times. This has been of particular significance in newborns where the prothrombin content is often low and the haematocrit value is a rule, partly, comparatively high, partly varies considerably from one child to the other, and in one and the same child, during different times. Thus the prothrombin values in newborns cannot be directly compared when the haematocrit values are not in agreement. The difference in the prothrombin time as between debile and fully developed newborns, as pointed out by several authors, may refer to conditions of this kind. Moreover, the fact that some authors have reached different results in this respect favours the possibility of such a source of error. However, this will be more closely ventilated in a later work.

In newborns, the haematocrit values often varies from day to day and this, of course, indicates that the prothrombin values

cannot be compared from one day to another without regard to the haematocrit values. As a rule, the amount of red blood corpuscles decreases and with it the prothrombin time during the first week of life. In this way, lower haematocrit values are obtained at the end than at the beginning of the week.

A few examples will be given below from an investigation now in progress of the manner in which the haematocrit values can change during the first week of life (cases a—d).

a. S. E.<sup>1</sup> 2601/1944, fem., day of birth 29/7. Weight at birth 3 820 grammes. Parturition and newborn period without remark. Haematocrit value 1/8: 61. 3/8: 51. 5/8: 48.

b. S.E. 2629/1944, male, day of birth 1/8. Weight at birth 3 330 grammes. Parturition and newborn period without remark. Haematocrit value 1/8: 80. 3/8: 60. 5/8: 58.

c. S. E. 2691/1944, male, day of birth 6/8. Weight at birth 3 430 grammes. Parturition and newborn period without remark. Haematocrit value 7/8: 57. 9/8: 54. 11/8: 50.

d. K. L. H. 837/1944, male. Day of birth 29/7. Weight at birth 3 130 grammes. Parturition and newborn period without remark. Haematocrit value 1/8: 61. 3/8: 51. 5/8: 48.

As seen from above, the haematocrit value may change to such an extent as to influence the prothrombin time. This fact must be taken into account in such an examination.

Further, similar to earlier examinations by Seoz, Bergami, and others, the present examination has shown that a latent prothrombin deficiency may occur (Cases 1, 3 and 9) when no definite prolongation of the prothrombin time has been ascertainable with the usual method but only appears after dilution of the plasma.

### Summary.

By removal of plasma from oxalate blood, as well as addition of plasma to it in one and the same person, the author has produced a dilution series of blood corpuscles-plasma, in other words, a series of blood tests with different haematocrit values. The

<sup>1</sup> S. E. = Hospital S:t Erik.

prothrombin time has been determined on these samples by means of Fiechter's method. It has then been found that a comparatively slight prolongation of the prothrombin time at increasing haematocrit values has taken place in the blood of healthy individuals. When, on the other hand, the prothrombin content in the blood has for some reason or other been reduced, the prothrombin time at increasing haematocrit values has undergone a palpable prolongation. Therefore, when a deficiency in prothrombin is suspected, the haematocrit values of those concerned must be taken into consideration. This should especially be born in mind in comparisons between the prothrombin times of infants. When a possible prothrombin deficiency is suspected and no distinct prolongation of the prothrombin time has been determined at the ordinary examination a plasma dilution may give the information required.

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FROM THE HOSPITAL FOR INFECTIOUS DISEASES, STOCKHOLM.  
HEAD: ROLF BERGMAN.

## **Inflammatory Processes in the Central Nervous System as a Complication of Scarlet Fever.**

By

**KARL-AXEL MELIN.**

Complications from the central nervous system do not infrequently occur in several of the most common infectious diseases. For instance, in a number of cases of morbilli, rubeola, varicellae and parotitis complications set in of a meningeal and, sometimes, also of an encephalitic type. In the case of virus diseases, no bacteria are ascertained in the lumbar fluid. Accordingly, it is inadequate to define these complications as aseptic. Purulent complications are rare. Moreover, when occurring, they never concern primary purulent cases of meningitis or meningo-encephalitis, but originate in an otitis, bronchopneumonia or something like that as a secondary effect.

The problem of the etiology of scarlatina is still far from solved. Many facts favour the conception that the hemolytic streptococci, as well as some as yet unknown virus, cause this disease through some kind of interplay. However, a direct neurotropia in the disease agents does not occur as, for instance, in the case of a morbilli virus, owing to the extreme scarcity of scarlatina complications from the central nervous system. As to the theories regarding the mode of appearance of the scarlatina, the above-mentioned complications can be divided, when of a primary nature, into two main groups, viz., septic ones due to hemolytic streptococci, and aseptic ones caused by virus. Furthermore, secondary complications may be added, many times of a septic kind, proceeding from, for instance, an otogenous or rhinogenous scarlatina complication.

The septic complications, primary ones as well as secondary, usually occur to a greater extent than the aseptic ones. In fact, during the course of the years most attention has been directed to them. The reasons for this are several. Thus, the conditions of the disease have, as a rule, been alarming, the course has been serious, the mortality rate high. In connection with the introduction of chemotherapeutics, active means were obtained for counteracting also these severe conditions of disease. Before then, therapeutical tests with polyvalent and type specific sera, as well as with scarlatina convalescentserum, had been adopted with much expectation.

The purely primary septic complications of the scarlatina within the central nervous system are rare. Several cases have been described in the literature. Nevertheless, agreement must be expressed with the contention presented by FORBES (1926) as follows: In connection with a report of a case of primary streptococcal meningitis in the scarlatina, where he was unable, in spite of all, to exclude the possibility of a latent otogenous infection as the source of origin, he points out that fewer cases of this type would without doubt be diagnosed if, at the autopsy, real pains were taken to trace the possible infectious foci. ZISCHINSKY (1930) also makes this suggestion in a description of a few cases of this type.

The majority of the meningeal affections do not, in this way, manifest themselves primarily from a general scarlatina pyaemia, but have some primary focus, located elsewhere in the organism, from which the infection then proceeds via the blood and lymph tracts, or directly from the infectious focus, to the meninges. Complications of this kind may occur at any time during the course of the disease, from the first days to far into the convalescent period. The otogenous processes most often cause the spreading of the infection. Thus, in a compilation made by GORDON and TOP (1935) 13 cases of purulent meningitis are discovered among 2 925 patients suffering from scarlatina and suppurative otitis. This corresponds to a frequency of 4.4 per thousand among otitis patients. The disease most often spreads directly via some bone destruction around the middle or inner

ear. Spreading from the sinus cavities of the nose comes probably next in frequency with regard to the mode of origin. In this particular case, the spreading occurs through the blood and lymph tracts, along fila olfactoria or directly owing to destruction of corticalis interna between the sinus cavities and the skull cavity. Spreading from distant individual foci rarely takes place. SCHOLLE (1904) mentions a case of meningitis where the primary focus was a suppurative gonitis. Further, GORDON and TOP (1935) describe two similar cases. EULENBURG (1859) relates a scarlatina patient in the convalescent stage who received a superficial injury of the skull. An infection set in and hemolytic streptococcal meningitis, which was the ultimate cause of death.

In contrast to the septic complications, the aseptic ones have been more sparsely represented in the literature in this field. The aseptic meningitis cases have been described in about ten works in all, while the still less frequent encephalitis cases have been mentioned in more than twice the number.

In 1899, PÄSSLER described the first diagnosed case of serous meningitis as a complication to scarlet fever. In 1900, STADELMANN gives an account of a similar case. PAISSEAU and MILHIT (1910) performed lumbar punctures on 32 scarlatina patients during the acute infectious stage. The cerebro-spinal fluid was normal in 23 of them. Two had a very severe scarlatina but no neurological symptoms. They had a moderate amount of lymphocytes in the cerebro-spinal fluid. Finally, 7 cases revealed meningism, but had very insignificant cerebro-spinal fluid findings. SACHS (1911) reports a series of cases from Berlin where he ascertained a meningism which was quite evident in 4 per cent of a series of 400 cases. The cerebro-spinal fluid findings were very sparse almost throughout the whole series. SCHACHTER (1936) and OLMER and LEGRÉ (1936) give accounts of individual cases of serous meningitis. These authors consider this complication to be exceptionally rare. In 1937, GORDON and TOP examined a material comprising 17 000 cases of scarlet fever from a hospital in Detroit. They found aseptic complications of different kinds, such as meningism, serous meningitis, encephalitis, in 30 of these patients. Thus, the frequency of this type of com-



plication in their material equalled 1.7 per thousand. STROE and BANU (1938) have collected 10 200 cases of the scarlatina in Bucharest. There they found a frequency of 1.3 per thousand as regards these complication. Their figures agree well those given by GORDON and TOP. Finally, LASSEN and BANG (1940) have made a compilation from a six-year material in Belgdamshospitalet in Copenhagen. Among 9 826 scarlatina patients, 20 cases of aseptic complications from the central nervous system were detected, corresponding to a frequency of, on an average, 2.0 per thousand. During the year 1939, however, particular attention was directed to this kind of complication. Consequently, during that year these complications were noted in not less than 14 out of 1 987 scarlatina patients, i. e. corresponding to 7.0 per thousand. This, as well as several of the fore-mentioned works, would imply that these complications are actually not so very unusual. They indicate rather that their course is generally so mild that both the patient and those in attendance have failed to take notice of them.

The encephalitic processes may be of two kinds, viz., either acute cerebral affections in connection with the primary stage of the disease, or signs of cerebral injury appearing during the period of convalescence. The former are, as a rule, transient and leave no complications whatever. They must, therefore, be regarded in the first place as toxical. The cases of encephalitis occurring later in the course of the disease are of a more serious nature. They are, in all likelihood, due to virus resulting not infrequently in permanent pareses or psychical disturbances.

Only a small number of the cases of encephalitis in the literature can definitely be referred to the scarlatina complications. SCHILDER (1919, 1928) tells of a girl of 21 years of age who was subjected to a severe encephalitis in the after-course of the scarlatina. He was in a position to re-examine her after nine years. She still suffered from serious defects in the region of the cerebral nerves and disturbances to motility in the arms. TOOMEY, DEMBO and CONNEL (1923) give a description of the course of the disease of a boy of 6 years who died three weeks after the exanthema stage in connection with severe cerebral symp-

tooms, with necrosis and hemorrhages in the brain. VAN BOGAERT, BORREMANS, REUSENS and WEYN (1932) reported two cases of encephalitis appearing late in the course of a scarlatina. One had complete restitution, the other slight disturbances to motility in the left arm which remained nine years afterwards. DUINKER (1932) describes a case where the encephalitis set in on the ninth day after the exanthema and the patient died. DAGNÉLIE and DUBOIS (1932) give an account of the course of a girl of 8 years, where the encephalitis occurred on the second day after the outbreak of the exanthema. Particularly the cerebellar symptoms were prominent and remained to a slight degree still four months after the onset of the illness. LEMIRRE and LAPLANE (1933) observed a bilateral ptosis which appeared on the ninth day after the exanthema of the scarlatina in the case of a woman of 27 years. The lumbar puncture gave the diagnosis of encephalitis. No new symptoms were added and on the 22nd day the patient did not reveal any signs of a complication from the central nervous system. FERRAND, SCHAEFFER and MARTIN (1935), DECOURT (1935), MORNET and VEZIN (1936) and MARTIN and CHAMPION (1937) present cases of a similar type which may all be regarded as definite scarlatina complications. In the above-mentioned compilation by GORDON and TOP comprising more than 17 000 cases, early, toxic cases of encephalitis, as well as encephalitis appearing in the late phases of the scarlatina, are included. 12 cases of the former and 11 of the latter are to be found in their material. Since only one of the last-mentioned cases has been described, the principles according to which they have classified their patients cannot be discussed. In LASSEN and BANG's compilation, also mentioned above, three cases of encephalitis were noted, all at an early period of the course of the scarlatina. Two of these instances disclosed at the after-examination neurological disturbances which might possibly be referable to the cerebral illness undergone earlier.

Among the patients treated at the Stockholm Hospital for Communicable Diseases on account of scarlet fever, complications of the type concerned in this paper have but rarely been observed. During the 20-year-period of 1925—1944, a total of 18 426 cases of this

disease have been admitted to this hospital. A complication from the central nervous system has been ascertainable only in 23 instances.

In a brief comparison between the complications in cases of the scarlatina, morbilli, rubeola, varicellae and parotitis, a marked difference is disclosed between the scarlatina, on the one hand, and the more common virus diseases enumerated above, on the other, considering the frequency of the neurological complications.

Table 1.

Disease	Time period	Total num. of cases	Neurological complication	
			Aseptic	Septic
Scarlatina . . . .	1925—1944	18 426	14	9
Morbilli . . . . .	1940—1944	1 397	13	0
Rubeola . . . . .	1937—1944	840	13	0
Varicellae . . . . .	1938—1944	733	4	0
Parotitis . . . . .	1938—1944	835	126	0

This tabular comparison is, to some extent, misleading, owing to the variations in the mode of origin of the figures denoting the total number of patients treated during a certain time period within the different disease groups. The majority of the scarlatina cases in Stockholm are submitted to treatment at the isolation hospital, whereas the other diseases referred to above are unaffected by the epidemic regulations. Accordingly, the cases admitted to the hospital have either been treated there for strong social indications or because the cases have rendered such a course advisable for purely medical reasons. However, in spite of these drawbacks with regard to the possibilities of direct comparison between the total figures, it is quite evident from the table that the neurotropia, mentioned introductorily, which occurs in virus, causing morbilli, rubeola, varicellae and parotitis, is of marked significance. In contrast with scarlatina, septic cerebral complications have not occurred in the other diseases within the respective time periods.

Purely primary septic complications have been noted in five cases in the examined scarlatina material. (See Table 2.)

Case num.	Journal num.	Sex, age	Onset of scarlatina	Ear complication	Time of meningitis symptom	Cerebro-spinal fluid			Remarks
						Cells per 1 mm <sup>3</sup>	LS/ba	Culture	
1.	633/1942	m. 25 yrs.	19/8	0	20/8	2230 (75 % polynuel.)	0.40	0 growth	9/8 healthy
2.	1422/1928	m. 1 yrs.	28/9	9/10 Ethmoiditis 16/10 Bilat. otit. + mastoidit.	13/11	5000 (90 % polynuel.)	—	Cocci	19/11 died
3.	2405/1933	m. 7 yrs.	18/11	23/11 Otit. No mas- toidit.	2/12	5030 (96 % polynuel.)	0.51	0 growth	9/12 died
4.	719/1927	m. 3 yrs.	16/8	6/4 Bilat. otit. + mastoidit.	20/4	7600 (Mainly polyn.)	—	Streptococci	22/4 died
5.	884/1940	m. 25 yrs.	25/8	0	25/8	19 (58 % polynuel.)	0.56	Haemol. streptococci	26/8 died

Table 3.

Case num.	Journal num.	Sex, age	Onset of scarlatina	Ear complication	Time of meningitis symptom	Cerebro-spinal fluid			Remarks
						Cells per 1 mm <sup>3</sup>	LS/ba	Culture	
6.	3172/1934	fem. 10 yrs.	20/10	20/10 Bilat. otitis 22/11 Mastoidit. + apicitis	20/11	2140 (46 % polynuel.)	0.23	Hemol. streptococci	2/12 died. Destruction of pars petrosa
7.	845/1937	m. 6 yrs.	23/8	2/4 Otitis 2/4 Mastoidit. + apicitis	2/4	13 600 (90 % polynuel.)	—	Pneumococci	2/8 died. Destruction of pars petrosa
8.	1450/1939	fem. 15 yrs.	The begin of March	19/3 Otitis 9/4 Mastoidit. Abscess of cerebellum	9/4	344 (48 % polynuel.)	0.64	—	12/8 healthy
9.	1936/1934	fem. 5 yrs.	1/7	2/7 Otitis 25/7 Mastoidit.	10/8	4100 (60 % polynuel.)	—	—	20/8 died

Case 1 had a metastatic, purulent meningitis which manifested itself at a very early phase in the course of the scarlatina. Hemolytic streptococci were never ascertainable in the lumbar fluid, since no cultures were made on a hemolytic plate. However, *inter alia*, the great quantity of polynuclears in the cerebro-spinal fluid and the comparatively low lumbar sugar-blood sugar quotient indicates the presence of bacteria in the cerebro-spinal fluid in this case. No aural or nasal complications were observed. The scarlatina pyaemia was, however, noticed owing to adenitis in the throat, possibly, also because of an acute hemorrhagic nephritis which turned up later. The hematuria may, nevertheless, have been due to the form of therapy administered, the patient having been given chemo-therapeutics in large doses during the acute phase of the meningitis.

Cases 2 and 3 are very similar to one another. The original disease was in both instances of a malignant type, involving complications in the shape of otitis and, in one case, in the form of a rapidly transient ethmoiditis. Mastoiditis developed out of the otitis but was drained by quick surgical intervention. In both cases, acute purulent meningitis set in during the after-course which rapidly lead to the death of the patients. In one of the cases, hemolytic streptococci were found in the lumbar fluid, in the other diplococci. Both the cases occurred before the chemo-therapeutic time. Accordingly, but little help was obtained from the therapeutical supplies at disposal. It is obvious that in these instances the aural complications occurring in the early stage of the disease and which were soon subjected to renewed surgery cannot in all likelihood be regarded as etiological factors of the meningitis. This was proved by the anatomical conditions established at operation in case 2, and at autopsy in case 3. Nor can the ethmoiditis which appeared very early in the course of the disease and was quickly healed have had any influence as an etiological factor. In these instances, an otitis and a meningitis are manifestations of processes of a similar type but without any direct etiological connection.

Case 4 concern a purulent meningitis, due to detected streptococci. In this particular case, otitis complicated the course of the scarlatina from the very start. When a morbilli also set in, the power of resistance of the patient became so reduced as to add serious complications to the ones already existing. Not at the autopsy of this case was any spreading *per continuitatem* of the infection from the ear to the meninges found. The meningeal process could be explained as an independent accessory phenomenon in the general scarlatina infection. In this latter case, it is possible that a spreading from the ear via the blood and lymph tracts has taken place. Finally, in case 5, patient fell ill in a malignant wound scarlatina occurring in connection with a surgical wound in the throat. Meningitis set in very quickly and, together with the other manifestations

of a general sepsis, caused the rapid death of the patient. A pronounced purulent meningitis never had time to develop. However, the presence of bacteria in the cerebrospinal fluid suffices to refer the case to this group.

In the remaining four cases of purulent meningitis, the infection had proceeded directly to the meninges from aural processes complicating the scarlatina. (See Table 3.)

Cases 6 and 7 conform very much with one another. Both suffered from very malignant otogenous processes which swiftly gave rise to apicitis and destruction of pars petrosa, thus opening the passage to the meninges for the infection. Case 8, which was complicated by an abscess in the cerebellum, occurred in the beginning of the chemotherapeutic stage. An active otological therapy combined with an intensive sulfanilamide treatment gave good results. Finally, as regards case 9, the ultimate course of the disease has not been fully elucidated owing to the fact that an obduction was never performable. However, the violent aural processes of the patient indicate that the infection had originated in those organs in spite of surgical therapy. Cases 6, 7 and 9 all occurred before the chemo-therapeutical time. Accordingly, the same possibilities of checking the development of the infection did not exist in these instances where the surgical therapy had been found unsatisfactory.

The cases of serous meningitis, 11 of which have been recorded, have for the greater part been either otogenous or rhinogenous. (See Table 4.)

All these cases have been subjected to a rapid, active otological therapy, in later years, combined with a sulfanilamide treatment. In this way the meningeal infection has been checked in its development and rapid recovery has ensued in all the patients.

In one case, a purely primary, lymphocytic meningitis occurred.

21. J. No. 1945/1944. A woman of 21 years. She had a swollen throat for 4—5 days. On 17/4, sudden general feeling of illness, temperature and severe troubles in swallowing. On 19/4, primary appearance of exanthema on the body. She was admitted on 20/4. She then had a typical scarlatina. Definite Schultz-Charlton reactions with regard to scarlatina convalescent serum as well as antitoxic streptococcal serum. Pharyngeal test showed hemolytic streptococci. Sed. rate 28 mm/1 hour. Subfebrile during the following days. She felt better every day subjectively. On 26/4, in the afternoon her temperature increased and she had a slight headache. Not stiff in the neck. On 27/4 40°, violent

Table 4.

Case num.	Journal num.	Sex, age	Onset of scarlatina	Ear complication	Time of meningitis symptom	Cerebro-spinal fluid			Remarks
						Cells per 1 mm <sup>3</sup>	Ls/lbs	Culture	
10.	1445/1934	m. 7 yrs.	12/5	12/5 Otitis 9/6 Mastoidit.	21/6	100 (12 % polynucle.)	0.72	—	11/8 healthy
11.	2333/1934	m. 9 yrs.	26/6	21/6 Otitis 4/6 Mastoidit. 10/6 Apicet	20/6	6 (10 % polynucle.)	0.64	0 growth	7/11 healthy
12.	3582/1934	m. 9 yrs.	20/11	21/1-35 Otitis 4/1 Mastoidit.	5/1	24 (33 % polynucle.)	—	0 growth	1/5 healthy
13.	3151/1937	fem. 34 yrs.	9/12	2/12 Otitis 17/12 Mastoidit. + labyrinthit.	17/12	8 (0 % polynucle.)	0.54	0 growth	2/5-38 healthy
14.	518/1938	m. 20 yrs.	2/2	Otitis 10/2 Mastoidit.	27/2	411 (53 % polynucle.)	—	0 growth	21/4 discharged as improved
15.	2010/1939	fem. 37 yrs.	5/4	12/4 Otitis 15/5 Mastoidit. + labyrinthit.	15/4	92 (61 % polynucle.)	0.71	0 growth	16/6 healthy
16.	3/1940	fem. 6 yrs.	22/2-39	1/1 Otitis 9/1 Mastoidit.	21/1	14 (15 % polynucle.)	—	—	22/2 healthy
17.	1109/1944	fem. 7 yrs.	2/2	2/2 Otitis 22/2 Mastoidit. 2/2 Extradural abscess	2/5	20 (25 % polynucle.)	0.68	0 growth	10/6 healthy
18.	1067/1928	fem. 5 yrs.	2/7	9/7 Ethmoidit.	12/7	660 (Mainly polyn.)	—	—	11/6 healthy
19.	2037/1939	m. 13 yrs.	15/5	15/4 Ethmoidit.	10/4	570 (41 % polynucle.)	0.38	0 growth	16/7 healthy
20.	786/1943	fem. 15 yrs.	16/2	28 Ethmoidit. + subperiosteal abscess	5/2	42 (50 % polynucle.)	0.21	0 growth	18/6 healthy



headache, pronounced stiffness in the neck, Lasègue positive at 45° bilaterally. Otherwise, nothing noteworthy in her nervous state. The aural state altogether normal. Lumbar puncture on 27/4: I. p. 350 mm. Clear, colourless cerebro-spinal fluid. Queckenstedt gave free deflexions. Pandy + Nonne +. Cells: 1 055/mm<sup>3</sup>, 3 % of which were polynuclear and 97 % mononuclear. Lumbar sugar/blood sugar = 47/148 mgr% = 0.31. Bacterial culture: No growth. Special culture on a hemolytic plate: No growth. Guinea-pig test: Negative. No tubercular bacillae in the sediment after centrifugation. On 28/4, somewhat improved. Less headache. No neurological finding of any importance apart from stiffness in the neck and positive Lasègue. Renewed lumbar puncture on 28/4: I. p. 160 mm. Clear cerebro-spinal fluid. Queckenstedt gave free deflexions. Pandy + Nonne traces. Cells: 497/mm<sup>3</sup> (mononuclear). Lumbar sugar/blood sugar = 52/120 mgr% = 0.43. Bacterial culture: No growth. Special culture on a hemolytic plate: No growth. On 1/5, no longer any stiffness in the neck. Nothing remarkable in the nerve status. Lumbar puncture on 2/5: I. p. not measurable. Clear cerebro-spinal fluid. Queckenstedt gave free deflexions. Pandy + Nonne traces. Cells: 69 mononuclear (200 red)/mm<sup>3</sup>. Lumbar sugar/blood sugar = 68/180 mgr% = 0.38. Bacterial culture: No growth. Special culture on a hemolytic plate: No growth. On 11/5, ring and lamellar peeling on hands and feet. On 7/6, she was discharged without any subjective or objective symptoms whatever apart from a slight tiredness. On 4/7 control: She still felt tired when doing intellectual work. Otherwise in full health.

Thus, in the above-mentioned case distinct signs of a meningitis were disclosed at a comparatively early stage of the disease, which was found to be of a lymphocytic type on examination. Repeated lumbar punctures and bacterial cultures on cerebro-spinal fluid did not offer any bacterial findings. The clinical picture as well as the development of the disease confirm the belief that no bacterial affection occurred in this particular case. No otogenous or rhinogenous complication was noted during the whole of the disease which was even completely free from complications in all respects save for the meningeal affection.

Finally, as regards the encephalitic disease conditions at scarlatina, two cases may be referred to here which belong to this group of complications:

22. J. No. 3372/1934. A boy of 14 years. He fell ill on 9/11 with a soar throat and a temperature 39°. On the following days, temperature, headache, a soar throat, vomiting fits. On 12/11 exanthema. He



was admitted to hospital. Typical scarlatina. Nothing neurologically remarkable. Definite Schultz-Charlton reactions both as regards scarlatina convalescent serum and antitoxic streptococcal serum. Pharyngeal tests showed no hemolytic streptococci. Since the temperature maintained a level of  $39^{\circ}$  during the day of admission and the next day, 10 ml of antitoxic scarlatina serum were administered. He was free from a temperature on the following day. Then, again slowly rising temperature. On 17/11  $39^{\circ}$ , no headache, but slight stiffness in the neck. Lasègue positive at approx.  $60^{\circ}$  bilaterally. Weak strength of pressure of the hand bilaterally. Lumbar puncture on 17/11: I. p. 205 mm. Clear cerebro-spinal fluid. Queckenstedt gave free deflexions. Pandy — Nonne +. Cells: 0. On 18/11 again falling temperature. No headache. Moderate stiffness in the neck. Still a slight weakness in the arms. Lasègue positive at approx.  $30^{\circ}$  bilaterally. Top peeling on the body. On 22/11 free from temperature. No symptoms from the central nervous system. Pronounced peeling during the following days. On 28/11 lumbar puncture (control): I. p. 150 mm. Clear cerebro-spinal fluid. Queckenstedt gave free deflexions. Pandy + Nonne —. Cells:  $10/\text{mm}^3$  (monocytes). Lumbar sugar/blood sugar =  $62/80$  mgr% =  $0.76$ . On 17/12, discharged free from symptoms.

23. J. No. 49/1932. A man of 25 years. He fell ill on 2/1 with swallowing trouble. 3/1 temperature. 7/1 exanthema. He was admitted to the hospital. Typical scarlatina with definite Schultz-Charlton reactions, both as regards the scarlatina convalescent serum and the antitoxic streptococcal serum. Hemolytic streptococci in repeated pharyngeal tests. On 12/1, a right-sided peritonsillitis was added with rapid recovery. A rise in the temperature to a good  $38^{\circ}$  in connection with it but otherwise free from temperature during the whole stay at the hospital. On 17/1, typical peeling on hand, arms and body.

28/1 i. e. on the 21st day after the exanthema, a slight, right-sided facialis paresis was noticed which receded again during the following days. On 2/2, a left-sided facialis paresis occurred, comprising all the three branches. This, too, receded although slower, and could not be detected any longer on 1/3. On 12/4, the patient was discharged as free from symptoms.

Lumbar puncture: On 5/2, I. p. 170 mm. Clear colourless cerebro-spinal fluid. Queckenstedt gave free deflexions. Pandy ++ Nonne +. Cells: 5 lymphocytes ( $200$  red)/ $\text{mm}^3$ . Lumbar sugar/blood sugar =  $78/80$  mgr% =  $0.98$ .

The first-mentioned case, where the slight encephalitic processes were ascertainable at an early phase in the course of the disease, belongs to the toxic group referred to in the literature

by, among others, GORDON and TOP. An observed effect on the brain sets in early, is generally of a mild nature, and disappears quickly without leaving any complications. The latter case which often manifests itself during the period of convalescence is of another kind. The complications are more serious and pareses and other neurological disturbances many times remain for long periods, perhaps even for life. In the last-mentioned case, the process has begun when the acute phase of the scarlatina has passed over. The left-sided facialis pareses remained for almost a month, then disappeared. No other neurological disturbances were noted.

When the results obtained in this compilation are summarized, the appearance of neurological scarlatina complications in the material examined in Stockholm will definitely be found to be rare. Among almost 18 500 scarlatina patients, only 23 revealed complications of this kind, 15 in direct connection with otogenous and rhinogenous processes, 8 without any ascertainable causative factor other than the scarlatina infection. When a comparison is made between the otogenous complications and GORDON and TOP's figures, it will be seen that, while they had 13 purulent, meningeal affections in a material of 2 925 scarlatina cases with otitis, corresponding to 4.6 per thousand of the cases, the Stockholm material of 2 826 scarlatina cases complicated by otitis had only 4 purulent meningitis patients, corresponding to only 1.4 per thousand. Without doubt, these low Stockholm figures may be attributed to the fact that an ear specialist, with all means for active therapy at his disposal, immediately takes care of the patients subjected to an otogenous complication during the course of the disease. The improved facilities for chemo-therapy have in later years rendered it easier to deal with these disease conditions. Provided sufficient attention is paid to the case, the infectious process will but rarely be of such a nature as to prevent the success of modern remedies in checking its development, when applied in time.

As regards the purely primary complications, they have also been very infrequent. However, the rareness of the primary

septic conditions have been testified by many. Thus, ZISCHINSKY only found six cases in a material exceeding 16 500 scarlatinas, a frequency well conforming with that of the Stockholm material. GORDON and TOP account for 21 cases in their material comprising over 17 000 patients. However, they do not make it clear whether the otogenous meningitis cases have been included in these calculations. If included, also their figures are in fair agreement with those published here. As regards the aseptic forms, the frequency figures from the various parts of the world vary greatly. However, the figures published by the majority of authors are considerably higher than those presented here. The present figures merely relate to one primary lymphocytic meningitis and two cases of encephalitis. Some mild meningeal complications may have been overlooked. This notwithstanding, the frequency of serious complications of this type must be regarded as remarkably low.

Finally, a few words should be said regarding the significance of these complications in the discussion of the etiology of the scarlatina. The septic forms, as well as the toxic early encephalitic cases, will be ignored in this connection. However, meningitis of a purely lymphocytic type, as well as encephalitis appearing during the convalescence, are unmistakably of the virus infection type. Thus, accepting the theory of the hemolytic streptococci as the sole cause of scarlatina, the appearance of these complications is difficult to account for. The explanation of these conditions as manifestations of poliomyelitis in scarlatina patients have, undoubtedly, been refuted by LASSEN and BANG. They made a comparison between the frequency of poliomyelitis in Denmark and the frequency of scarlet fever complications of the type in question, and found no agreement whatsoever. The cases described by the present author favour the same contention, having occurred at times when poliomyelitis has not occurred at all. Complications of this kind must, consequently, be said to confirm the conception that, in addition to the hemolytic streptococci, some other infectious substance, a virus for instance, must be coupled to the mechanism of origin of the scarlet fever.

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## **On Casein from Human and Cow's Milk and their Behaviour on Hydrolysis with Different Proteolytic Enzymes.**

**(Preliminary Report.)**

By

**OLOF MELLANDER.**

The nutritional difference between human and cow's milk is well known, but so far no evident reason for the difference has been found in the chemical composition in the two types of milk. With regard to the protein characteristic of milk, i. e. casein, the common opinion has been that there are only small differences between caseins derived from the milk of different species (1). Casein belongs to the relatively small group of proteins that contain phosphorus as a part of the protein molecule. Other proteins belonging to this group are vitellin found in birds' eggs and ichtulin from fish eggs. Like casein the latter are also used for nutrition purposes during early life. During these stages of development it seems important that phosphorus is supplied to the organism in organically (to protein) bound form. Compared with casein from cow's milk, casein from human milk has been rather incompletely investigated in several respects. The mechanism for the digestion of human milk casein by the different proteolytic enzymes of the intestine is little known. During digestion of casein from cow's milk with trypsin a fraction resistant to further action of the enzyme is formed. It is not known whether human milk casein behaves in a similar manner.

As these problems are evidently very important for the nutrition of the infant and are also of great theoretical interest, the author is at present investigating human and cow's milk casein

Table 1.

Elementary Analyses of Casein from human and cow's milk.

	Carbon %	Hydrogen %	Nitrogen %	Phos- phorus %	Sulfur %	Oxygen %
<i>Human casein:</i>						
WRÓBLEWSKI (3) . .	52.24	7.32	14.97	0.68	1.12	23.66 (by differ- ence)
LANGSTEIN and BERGELL (4) . . .			14.34	0.27	0.85	
BOSWORTH and GIBLIN (5) . . . .			15.75	0.70	0.70	
The author <sup>1</sup> . . . .	53.50	7.14	15.13	0.46		
	53.73	7.20	15.11	0.47		
	53.73	7.13	14.83	0.47		
<i>Cow's casein:</i>						
HAMMARSTEN (6) . .	52.96	7.05	15.65	0.85	0.72	22.77 (by differ- ence)
VAN SLYKE and BOS- WORTH (7) . . . .	53.50	7.13	15.80	0.71	0.72	22.14 (by differ- ence)
RAMSDELL and WHIT- TIER (8) . . . . . (casein separated from milk by means of the Sharples super-centrifuge)	52.88	7.00	15.51	0.79	0.77	23.05 (by differ- ence)

<sup>1</sup> The authors figures on an ash-free and moisture-free basis. Analyses performed by Mr. W. KIRSTEN.

in some chemical respects expected to be important from the nutritional point of view. Another interesting question is whether any difference in the course of the proteolytic hydrolysis of the two types of casein influences the ability of the infant to utilize cow's milk and human milk respectively.

The human milk casein used in the present investigation was prepared from fat-free human milk, which was diluted with twenty volumes of water, whereupon the casein was easily precipitated by adding 0.05 N hydrochloric acid to pH 4.6 and

Table 2.

Amino Acid Composition of casein from human and cow's milk according to WILLIAMSON (9).

Amino acid	Human casein %	Cow's casein %
Tyrosine . . . . .	5.5	5.5
Alanine . . . . .	2.0	2.3
Glycine . . . . .	0	0.4
Proline . . . . .	8.9	8.1
Glutamic acid . . . . .	20.9	21.9
Aspartic » . . . . .	4.6	4.2
Serine . . . . .	5.4	5.0
Cystine . . . . .	0.6	0.4
Arginine . . . . .	3.4	3.9
Phenylalanine . . . . .	5.8	5.5
Leucine . . . . .	12.2	14.4
Isoleucine . . . . .	6.3	5.2
Histidine . . . . .	2.0	2.0
Lysine . . . . .	5.6	6.0
Threonine . . . . .	4.5	4.6
Methionine . . . . .	2.3	3.1
Tryptophane . . . . .	1.5	1.3
Valine . . . . .	5.0	5.3

warming to 35° C. The precipitate was repeatedly washed with water, and the water then removed by rapid treatment with ethanol in increasing concentrations. The product was finally treated with ether, and the casein thus obtained dried in vacuo over calcium chloride at 35° C. The casein prepared in this manner is a finely divided white powder. Casein from cow's milk was prepared as described by LINDERSTRÖM-LANG (2).

The analytical data of the human milk casein prepared as above, together with some analytical data of human and cow's milk casein, are shown in table 1. As may be seen, there are but

small differences between the two types of casein except with regard to the phosphorus content. The latter varies considerably in earlier preparations of human casein, but in my own it lies fairly constant at about 0.47 %, i.e. at a figure slightly above half of that for cow's casein.

The amino acid composition of human milk casein has recently been investigated by WILLIAMSSON (9). As his paper is rather difficult of access here, his results are given in table 2.

As may be seen from the table the amino acid composition of the two types of casein is very similar.

### *The Homogeneity of Casein.*

The inhomogeneity of cow's casein has been shown in several ways by earlier investigators. By treatment with alcoholic hydrochloric acid LINDERSTRÖM-LANG (2) fractionated casein from cow's milk in several components which differed from each other mainly in their phosphorus content. The latter varied between 0.11 and 0.96 %. If these fractions are mixed together again a product is obtained which resembles the original casein in several respects, although it seems possible that the relatively rough treatment causes irreversible changes in the protein molecule. Studies by means of the ultracentrifuge have also shown that cow's casein is not a homogeneous substance (10).

The electrophoretic technique developed by TISELIUS (11) offers a very gentle method for studying the homogeneity of proteins and for the separation of electrophoretically different fractions.<sup>1</sup> The principle is that electrochemically different proteins or protein components in an electric field migrate at different speeds, and thus may be separated from each other. The fastest- and the slowest-moving components may usually be isolated in their pure form. The different migrating boundaries of the components are conveniently made visible on a screen or recorded on a photographic plate by the method devised by SVENSSON (13). In the diagrams thus obtained each component

<sup>1</sup> For details of the technique used, the reader is referred also to the monograph by ABRAMSON, MOYER and GORIN (12).



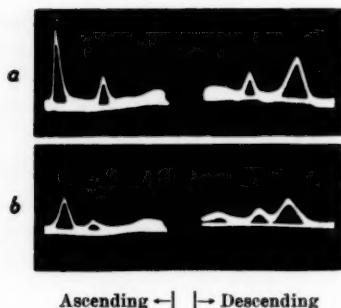


Fig. 1. Electrophoretic patterns of cow's casein (a) and human casein (b). Phosphate buffer at pH 7.62. Ionic strength 0.15 (phosphate 0.10 + sodium chloride 0.05). C.a 5 volts/cm. Concentration of casein 1 %.

is represented by a peak, and the area of the peak is proportional to the concentration of the component in the original protein solution.

An electrophoretic study of cow's milk casein carried out by the author (14) some years ago showed that this protein was electrophoretically inhomogeneous. The electrophoretic diagram (fig. 1 a) shows three peaks which were assumed to correspond to three different casein fractions, designated  $\alpha$ -,  $\beta$ - and  $\gamma$ -casein respectively. The fastest-moving component, the  $\alpha$ -casein was isolated, and on analysis it was found that its phosphorus content was higher than that of the original casein (table 3). It seems likely that the higher velocity of this component is due to its higher negative charge, caused by its larger content of phosphorus in the form of phosphoric acid radicals. These results have recently been confirmed by WARNER (15), who also prepared pure  $\alpha$ - and  $\beta$ -casein by means of precipitation at different pH.

Electrophoretic analysis of human milk casein has shown that this casein, also, is inhomogeneous (fig. 1 b). The electrophoretic pattern shows three peaks. The two fastest of these represent without doubt two distinct casein fractions, while the third may, at least in part, be due to a boundary anomaly. This may possibly also be the case with the corresponding peak (' $\gamma$ -fraction') of cow's casein (Cf. WARNER loc. cit.). The

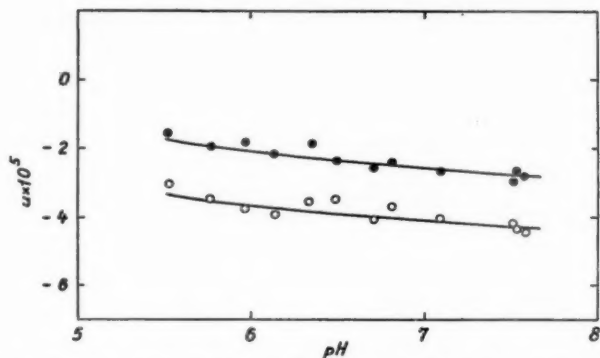


Fig. 2. Electrophoretic mobilities, in  $\text{cm}^2 \text{V}^{-1} \text{sec}^{-1} \times 10^5$ , of human  $\alpha$ - and  $\beta$ -casein ( $\alpha$ -casein  $\circ$ ,  $\beta$ -casein  $\bullet$ ) at different pH. Phosphate buffer, ionic strength 0.15 (phosphate 0.10 + sodium chloride 0.05).  $C_a$  5 volts/cm. Concentration of casein 0.5 %. Temp.  $0.0^\circ \text{C}$ .

$\alpha$ -fraction of human casein has been isolated electrophoretically and, as is shown in table 3, has been found to possess higher P/N-ratio than the original casein. The table also shows that the difference in phosphorus content between the  $\alpha$ -fraction and the original casein is more pronounced in human than in cow's milk casein.

Table 3.

Analytical Data on Casein and  $\alpha$ -casein from human and cow's milk.

	% N	P/N	% P*
Human casein I . . .	15.11	0.031	0.47
» $\alpha$ -casein I . .		0.058	0.87
Human casein II . .	15.14	0.030	0.46
» $\alpha$ -casein II . .		0.063	0.95
Cow's casein . . . .	15.66	0.052	0.81
» $\alpha$ -casein . . . .		0.061	0.96

\* (Assuming the same nitrogen content in  $\alpha$ -casein as in original casein.)

The migration velocity for the  $\alpha$ - and  $\beta$ -fractions of human milk casein at varying pH is shown in fig. 2. Electrophoretically,

there is thus no pronounced difference between human milk- and cow's milk casein. As mentioned above a difference in the relative phosphorus distribution between the  $\alpha$ -fraction and the rest of the casein seems to exist, however. In the human casein the  $\alpha$ -fraction contains a greater part of the total casein phosphorus.

*The Mechanism of the Enzymatic Hydrolysis of Casein.*

Already in 1894 WRÓBLEWSKI (3) found a pronounced difference in the action of pepsin on human and cow's casein. During peptic digestion of cow's casein there was very soon formed a jellylike clot, which was not observed during the digestion of human casein. Swine pepsin or pepsin prepared from children's stomachs behaved in the same manner. This suggested to WRÓBLEWSKI that there was an essential difference in the structure of the two caseins. The peptic and tryptic digestion of cow's casein has been studied by several investigators while, as far as the author knows, that of human casein has, after WRÓBLEWSKI, hardly been studied at all. Some years ago HOLTER, LINDERSTRÖM-LANG and FUNDER (16) studied the digestion of cow's casein with pepsin. As substrate, casein and casein fractions prepared according to LINDERSTRÖM-LANG were used. It was found that the casein fractions exhibited a different resistance towards pepsin, and that the fractions with the highest phosphorus content were more easily broken down. These authors also showed that the changes in viscosity during peptic digestion, which changes had been observed earlier by WALDSCHMIDT-LEITZ and SIMONS (17), showed a characteristic course for different casein fractions when digested by the same pepsin preparation under the same circumstances. The viscosity curve during digestion of cow's casein is shown in fig. 3. The experiment was performed in a manner very similar to that used by HOLTER, LINDERSTRÖM-LANG and FUNDER. The progress of the proteolysis was followed by formol titration with 0.05 N sodium hydroxide, carried out in an atmosphere of nitrogen using the titration apparatus designed by STENHAGEN (18). The viscosity was determined with an ordinary Ostwald viscosimeter. The agreement between the author's curve and that of HOLTER,

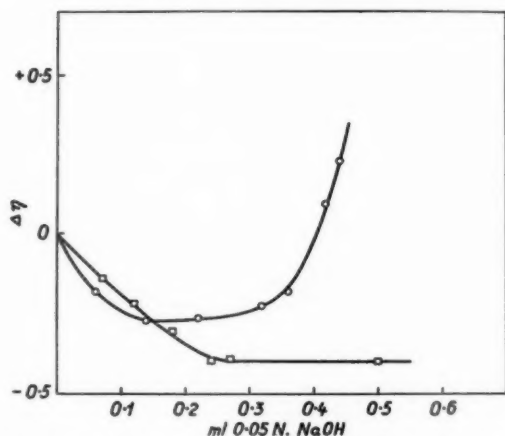


Fig. 3. Change in relative viscosity ( $\Delta\eta$ ) during hydrolysis of cow's casein (○) and human casein (□) with pepsin. Hydrolysis registered by formol-titration (ml. 0.05 N. NaOH). Concentration of casein ca 2 % and of pepsin 0.05 % (Parke Davis & Co.  $1/8000$ ). Temp. 30° C.

LINDERSTRÖM-LANG and FUNDER is very good. In the early stage of the digestion the viscosity of the casein solution decreases and passes through a minimum, and then increases rapidly. If the digestion is continued a jelly clot is formed, 'pseudo- or paranuclein'. According to HOLTER, LINDERSTRÖM-LANG and FUNDER the initial decrease in the viscosity is analogous to the decrease ordinarily found during the digestion of proteins. The latter increase, however, is characteristic of cow's casein, and probably caused by an incipient precipitation of the paranuclein. Similar experiments have now been carried out with human casein under the same conditions. In this case, too, a decrease in the viscosity in the early stages of digestion was observed, but the increase characteristic of cow's casein is entirely absent (fig. 3). Instead, the viscosity falls to a constant level. During the later stages of digestion no clot or gel was observed, which agrees with the experience of WRÓBLEWSKI. As both the formation of paranuclein and the increase in viscosity are not forthcoming, the experiment supports the view of HOLTER, LINDERSTRÖM-LANG and FUNDER that the viscosity increase is due to the paranuclein formation.

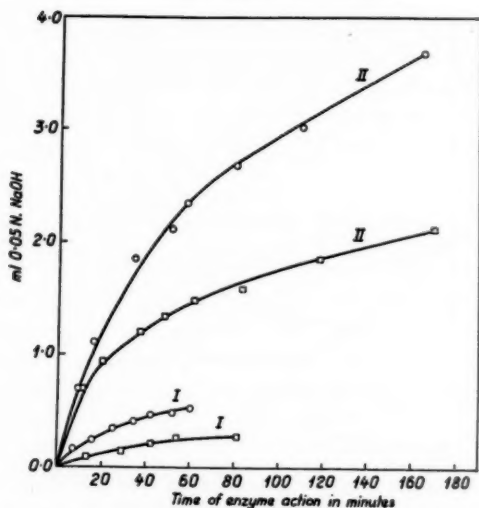


Fig. 4. Hydrolysis of human (□) and cow's (○) casein with pepsin (I) and trypsin (II). Hydrolysis followed by formol-titration (ml. 0.05 N. NaOH).

OTILIE BUDDE (19) has shown that gastric juice from infants (obtained after tea test meal) or swine pepsin digest the proteins of cow's milk (using fat-free milk as substrate) more rapidly and to a higher degree than when human milk is used as substrate. The same difference was observed by BUDDE and FREUDENBERG (20) in digestion with trypsin instead of pepsin. This remarkable difference is not easy to reconcile with the common opinion that human milk should be easier to digest than cow's milk. BUDDE and FREUDENBERG suggest that the difference is due to the higher relative albumin content of human milk, as they have demonstrated that the albumin of cow's milk is less easily hydrolysed by pepsin than is the casein. They conclude that the albumin of human milk is also digested with greater difficulty, and suggest that the albumin of human milk is resorbed from the intestines without being completely hydrolysed into amino-acids. It might be pointed out in this connection that the results of BUDDE and FREUDENBERG may also be explained by the assumption that human milk and cow's milk casein differ

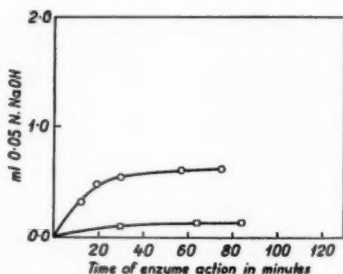


Fig. 5. Hydrolysis of human ( $\square$ ) and cow's ( $\circ$ ) casein with gastric juice from an adult person. Hydrolysis followed by formol-titration (ml. 0.05 N. NaOH).

in their behaviour towards proteolytic enzymes. That a difference of this kind really exists is evident from the following experiment. To a 2 % solution of cow's casein and human casein respectively, at the same pH (2.20) and with the same salt conditions, was added pepsin (Parke Davis 1/3000) to a concentration of 0.05 %, and the mixture allowed to digest at a temperature of 30° C. The hydrolysis was followed by formol titration as described above. From fig. 4 (I) may be seen the degradation after e.g. 60 minutes was found to be about twice as large for cow's casein as for human casein. Also in digestion with trypsin (Difco commercial preparation 1/110) a pronounced difference of the same kind is found (fig. 4 (II)). Gastric juice (obtained from an adult after injection of histamine) gives a similar result (fig. 5). It seems quite clearly established that there is a real difference in the behaviour of the two types of casein towards pepsin and trypsin. It is interesting to compare these results with those obtained by HOLTER, LINDERSTRÖM-LANG and FUNDER (16) when digesting casein fractions of different phosphorus content. The cow's casein with its higher phosphorus content is hydrolysed more rapidly than the casein of human milk, that is to say, in this case, too, the casein of highest phosphorus content is broken down most easily.

The behaviour of the different casein fractions during digestion has been followed also electrophoretically. As shown in fig. 6 I the  $\alpha$ - and  $\beta$ -peaks disappear almost completely during pepsin hydro-

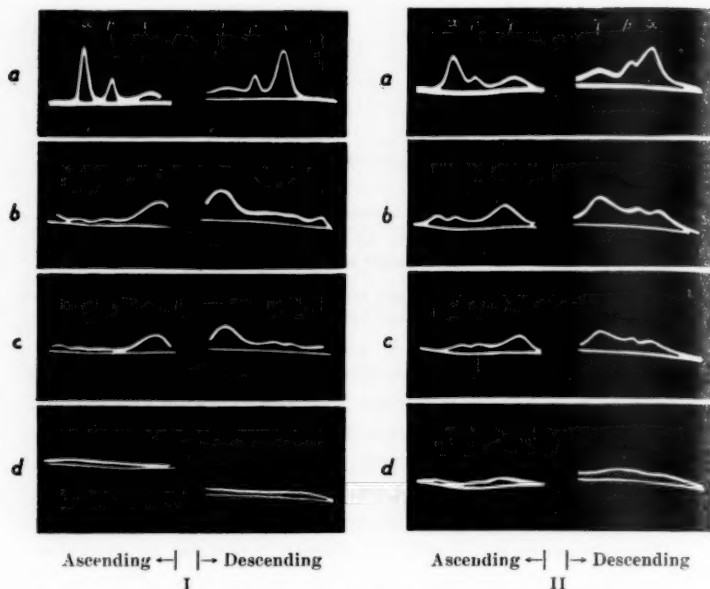


Fig. 6. Electrophoretic patterns obtained at different stages of pepsin and trypsin hydrolysis of cow's (I) and human (II) casein. *a*) without pepsin<sup>1</sup>, *b*) after peptic digestion during 109 hours, *c*) after peptic digestion during 123 hours (no further increase in amino-N), *d*) after tryptic digestion till constant amino-N (about 9 hours). In all electrophoretic experiments phosphate buffer at pH 7.45, ionic strength 0.25 (phosphate 0.05 + sodium chloride 0.20).

lysis of cow's casein. In the case of human casein, however, small peaks still remain (fig. 6 II). In the course of the digestion there is also formed a new fraction on the site of the  $\gamma$ -peak of the original casein. If the peptic digestion is followed by a tryptic one (fig. 6 I, II) all peaks in the electrophoretic diagram disappear. The electrophoretic pattern of cow's casein in the very beginning of pepsin hydrolysis is shown in fig. 7. The first

<sup>1</sup> The casein solution used in this experiment was made up several days before the electrophoresis was run. The pattern is identical with that of a freshly prepared casein solution. It is thus evident that the casein itself does not contain any proteolytic enzymes of importance in this connection.

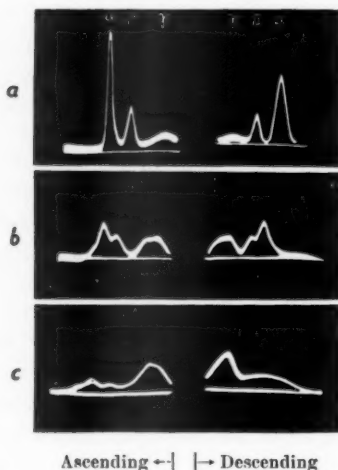


Fig. 7. Electrophoretic patterns of cow's casein after digestion with pepsin during a) 0, b) 18, c) 198 minutes. In all electrophoretic experiments phosphate buffer at pH 7.45, ionic strength 0.25 (phosphate 0.05 + sodium chloride 0.20).

changes observed are a decrease of the  $\alpha$ -, and to some extent also of the  $\beta$ -peak, and the formation of the new fraction mentioned above.

#### *Preparation of a Trypsinresistant Phosphopeptone from Human Milk Casein.*

By means of tryptic digestion POSTERNAK (21) was able to isolate a series of substances from cow's casein, which he called lactotyrynes. These fractions were resistant to further tryptic action, and possessed a relatively high P/N-ratio. RIMINGTON (22) and others have later isolated similar substances, which they called trypsin-resistant phosphopeptones. DAMODARAN and RAMACHANDRAN (23) have described a method of preparation which gives phosphopeptones of constant composition. The casein is digested with pepsin until no further hydrolysis occurs, and the paranuclein thus obtained (containing 50—60 % of the phosphorus and only about 20 % of the nitrogen of the original casein) is then digested



with trypsin till constant amino-N is reached. The remaining phosphorus-containing organic complex is precipitated by means of lead acetate, redigested with trypsin, and finally precipitated from the digestion mixture as barium salt. The preparations thus obtained had a constant composition and contained the following amino-acids, viz. 3 mol. of glutamic acid, 3 mol. of isoleucine and 4 mol. of serine. The composition of the barium salt is shown in table 4. Following the preparation method of DAMODARAN and RAMACHANDRAN, with minor modifications, the author has been able to isolate a similar fraction from human milk casein also. From the data given in table 4 it appears that its nitrogen and phosphorus content is very similar to the corresponding compound isolated from cow's casein. Owing to the small amount so far obtained, it has not yet been possible to carry out a complete amino-acid analysis. DAMODARAN and RAMACHANDRAN give no figure for their final yield of phosphopeptone. The author obtained from 25 g human casein c. 1.5 g phosphopeptone (as Ba salt), and about the same yield from cow's casein.

These trypsin-resistant fractions from cow's and human milk casein might, on account of their high phosphorus content, be expected to be identical with the electrophoretically isolated  $\alpha$ -fraction, but the digestion diagrams in figs. 6 and 7 show that this cannot be the case as the  $\alpha$ -fraction disappears during the digestion.

Table 4.

Analytical Data on Ba phosphopeptones.

	N %	P %	Ba %
From cow's casein (DAMODARAN and RAMACHANDRAN) . . . .	6.39—6.48	4.26—4.58	33.12—34.02
From human casein . . . . .	6.57	4.28	33.6

### Discussion and Summary.

By means of electrophoretic analysis it has been possible to separate human milk casein, as previously cow's casein, into two or possibly three fractions. The fastest-moving, the  $\alpha$ -casein, contains more phosphorus than the original casein. A relatively larger part of the total casein phosphorus is found in the  $\alpha$ -fraction of human casein as compared with cow's casein. Digestion experiments using pepsin, trypsin and gastric juice from an adult person show a considerable difference in the digestibility, cow's casein being more readily and more completely hydrolysed than human casein. BUDDE and FREUDENBERG have earlier shown that such a difference exists between whole human and cow's milk. These authors considered that the difference was due to the different relative albumin content in the two types of milk. It is evident, however, that it may also be explained by the greater resistance to pepsin and trypsin here found for human casein. It thus appears as if the casein of the no doubt nutritionally more valuable human milk is more resistant to enzymatic hydrolysis with pepsin and trypsin than is cow's milk casein. It should be remembered, however, that we know little about the physiological digestion in the intestine. Nevertheless, the isolation of phosphopeptones, resistant to trypsin<sup>1</sup> from human as well as cow's casein indicates that part of the casein probably is resorbed in the form of phosphorus-containing, larger amino-acid complexes. The molecular weight of the cow's casein phosphopeptone (about 1500) probably does not prevent resorption through the intestinal wall. It is noteworthy that these phosphopeptones contain a relatively high per cent of phosphorus, which cannot be removed by proteolytic ferments but is easily split off by different phosphatases as shown by RIMINGTON and KAY (24). It seems reasonable to suppose with these authors that the existence of this organically bound phosphorus, protected against the action of intestinal ferments, guarantees the admission of a certain amount of phosphorus to the growing organism. The organically bound

<sup>1</sup> According to DAMODARAN and RAMACHANDRAN the phosphopeptone from cow's casein is resistant also to intestinal erepsin.

phosphorus is prevented from forming insoluble calcium salts, which cannot be resorbed. In order to make this phosphorus available to the organism, it is of course necessary that a splitting of the phosphopeptone occurs *after* resorption from the intestine. Such a splitting might be imagined to take place in the epiphyses themselves, which are known to contain fairly large amounts of phosphatase. According to ROBISON (25) this bone phosphatase plays an essential part in ossification. It is assumed to hydrolyse organic phosphorus esters in blood, liberating inorganic phosphate. The phosphopeptones from casein might possibly be a convenient substrate to the bone phosphatase also *in vivo* and perhaps this enzyme is more active against phosphopeptones derived from casein of the same species. This view is supported by the fact that KELLER (26) has found urine from cow's-milk-fed infants to contain a higher percentage of organically bound phosphorus than does urine from breast-fed infants. The relatively weak action of rat-bone-phosphatase against phosphopeptone from cow's casein observed by RIMINGTON and KAY is also interesting in this connection. If a difference in the activity of bone-phosphatase to phosphopeptones from different caseins really exist it would reasonably explain why human milk has a better antirachitic action for infants despite its lower phosphorus and calcium content. It is possible that the mechanism outlined above is of special importance in cases where the resorption conditions for inorganic calcium and phosphorus are poor, e.g. owing to deficiency of vitamin D. The action of infant blood- and bone-phosphatase on different phosphopeptones is being investigated by the author.

This work has been supported by grants from the Andersson, the Lindahl and the Lennander Foundations and by »Svenska Sällskapet för Medicinsk forskning».

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## **The Stockholm Centre for Distribution of Mothers' Milk.**

By

**ULF NORDWALL, M. B.**

During recent years it has become increasingly difficult to obtain wet-nurses in Sweden, as a result of the laws regarding the care of babies. This has especially been felt at the Babies' Hospitals. By the establishment of the Centre for Distribution of Mothers' Milk, which acts as agent between mothers who produce more milk than their own babies can consume, and other babies — especially sick ones — who are in need of it, an attempt has been made to overcome this shortage.

The Stockholm Centre for Distribution of Mothers' Milk commenced its activities in the autumn of 1940 and the experience gathered during the first few years is given here. Even earlier than 1940 a similar organisation had been in existence, though on a smaller scale, at the Crown Princess Lovisa's Children's Hospital in Stockholm, where a number of methods, previously used in Erfurt (Dr. E. Kayser), had been tested. The Centre now in existence, which is run by Doctor Rudolf Ullmark and the author, has its Laboratory and testing rooms for mothers at the Milk Centre, the largest milk and dairy-product sales organisation in Stockholm, that places free of charge its resources at the disposal of Mothers' Milk Distribution Centre.

The collection of milk from the mothers and the distribution of it to the consumers is effected by means of the Milk Centre's own cars, which are in daily contact with Children's Hospitals etc. and approximately 3 000 shops in Stockholm and the suburbs where the Milk Centre delivers milk. Mothers' milk is delivered

first and foremost to Children's Hospitals and Babies' Institutes and then, according to the supply available, to private persons who, against Doctors' certificates may have mothers' milk.

The suppliers leave their milk every day at the nearest milk shop, where they exchange full bottles for clean ones sent from the Mothers' Milk Distribution Centre. The same method is used for consumers to collect the milk — the empty bottle is exchanged for a filled one sent from the Distribution Centre.

Mothers' milk is bought from the Milk Centre for four Swedish crowns and sold for six Swedish crowns. For the less well-to-do, the Town of Stockholm has made a grant for the purchase of mothers' milk.

Before a woman is allowed to supply mothers' milk, she undergoes a thorough examination free of charge, including an X-ray of the lungs and the Wassermann test.

All milk is tested for possible acidity. Litmus paper is used for a preliminary test and then Lyphan paper if necessary, which immediately shows an approximate Ph. value. A value of Ph. = 5.8 has been set as a limit for milk acceptable.

Twice a week the milk is tested for dilution with cows' milk or water. Dilution with cows' milk is disclosed by means of a precipitate reaction, when serum from rabbits, who have been injected with cows' milk is used. The method is simple and results clearly in a rash for the slightest dilution. Dilution with water is controlled by establishing the specific weight and fat content, the latter by means of the sulphuric acid method.

After the milk has been measured and tested, it is pasteurized — heated to a temperature of 68 degrees Celsius for ten minutes. It is then strained and cooled. The milk that is to be stored for any length of time is frozen in the refrigerator room to about  $-20^{\circ}$  Celsius. When supplies are plentiful, dried milk has also been prepared.

There is intimate cooperation between the Mothers' Milk Distribution Centre and the Children's Care Centres in Stockholm. The recruiting of mothers willing to give milk — except at maternity hospitals — is done to a great extent at the Children's Care Centres. Within their normal work is included inspection

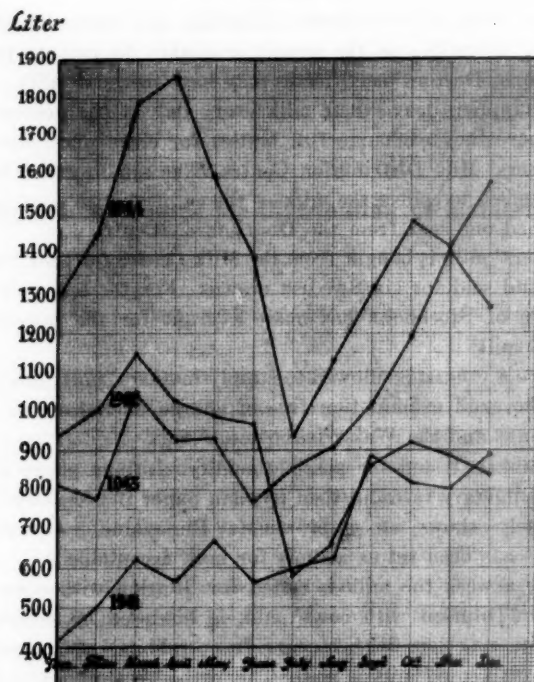


Diagram 1.

of hygiene in the homes and of the children's state of health. Reports on this are sent to the Milk Distribution Centre.

During the few years that the Milk Distribution Centre has been working, the activities have rapidly increased, as is shown in the following table:

Year	Milk received	No. of new suppliers registered
1941	7 959 litres	308
1942	10 903 "	407
1943	12 135 "	469
1944	17 282 "	601

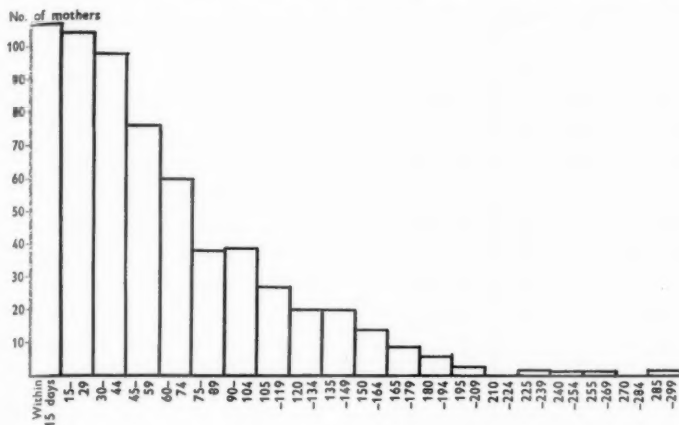


Diagram 2. No. of days during which mothers gave milk.

Both the figures for newly-registered mothers willing to give milk and the amount of milk received have therefore been approximately doubled during these four years.

The amount of milk during the months of the year is illustrated by Diagram 1.

The graphs show that the delivery of milk during the different months varies greatly. The decrease during the summer months is noticeable, coinciding with the holiday period. Experience has shown that after propaganda in the Press, registration of donors to the Milk Distribution Centre has increased. No biological reason can therefore be given for the variations in the supply of milk shown in the diagrams.

From the practical point of view, these variations are inconvenient, as the need of mothers' milk is much more constant. During the »good periods», therefore, not all the milk received can be distributed, but some must be stored. A reserve, comprising some hundreds of litres, should preferably always be available.

Of the total amount of mothers' milk distributed during the year 1941, 44 %, and during the years 1942—44, 38—39 %, went to Children's Hospitals and Babies' Centres in Stockholm. The



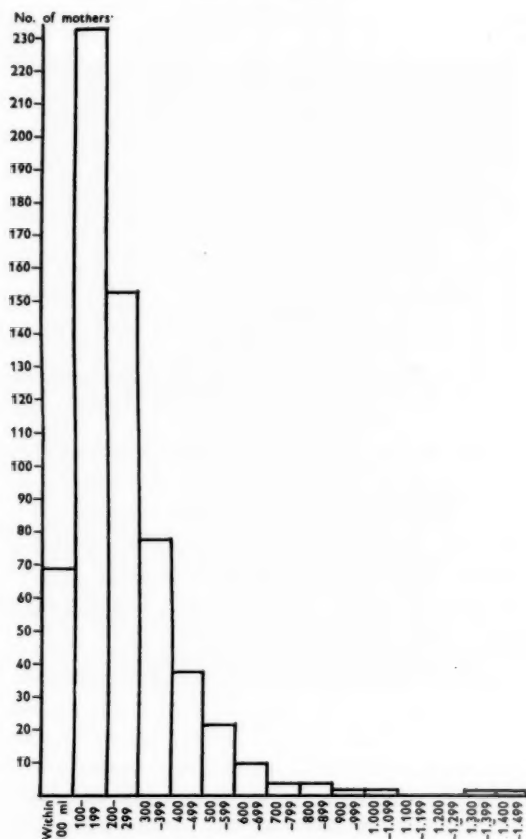


Diagram 3. Average quantity in millilitres per mother and day.

remainder was sold to private consumers. These were in 1941 216 and in 1944 479.

The period during which mothers give milk to the Centre is shown in Diagram 2. It also shows that relatively few give milk for more than three to four months. The research was made with 626 mothers.

Diagram 3. shows the average quantity per day and mother

in millilitres. The greater number give, as is shown, between 100 and 400 millilitres per day.

Research has been made concerning the quantity of milk delivered amongst 616 women of different ages. Women aged from 16—43 years have delivered milk. Women over 36 years old have been relatively few and have mostly given less milk than the other age groups.

The mothers giving milk have roughly been divided into three groups: I — Upper Middle class, II — Lower Middle class, III — Working class. During the years 1940 to 1943, 1 087 mothers have been registered. Of these 258 belonged to group I, 286 to group II and 543 to group III. It is therefore apparent that almost exactly half belong to the working classes.

### Summary.

A short account of how the Stockholm Centre for the Distribution of Mothers' Milk is organised, and the methods used at the Centre for supervision and pasteurization of milk. Figures are given, showing the rapid development of the Centre during its existence of little more than four years, the quantity of milk collected, and how long mothers continue to deliver milk to the Centre. An attempt has also been made to divide the mothers who give milk into their social classes.

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FROM THE PEDIATRIC CLINIC OF KAROLINSKA INSTITUTET AT NORR-  
TULL HOSPITAL, STOCKHOLM. HEAD: PROF. ARVID WALLGREN, M.D.

## **The Occurrence of Erythema Nodosum in Children with Primary Tuberculosis, treated with Sulfatiazol.**

### **Preliminary Report.**

By

**SVEN-IVAR ROLLOF,**

Med. Lic.

During the last few years, largely owing to the development of sulfacomounds, the discussion on the subject of Erythema Nodosum (E. N.) has been carried into new fields. After a number of earlier studies in which different theories had been advanced regarding its etiology, such as rheumatic diseases (MACKENZIE (1), HEGLER (2), SCHUMACHER (3), WEINTRAUB (4), WIBORG (5) and others), tuberculosis, specific agents (Trousseau (6), JOCHMANN-HEGLER (7), TACHAU (8), SYMES (9), FORNARA (10), ROSENOW (11) and others), investigators seem to have finally agreed to view E. N. as an allergic skin reaction, induced by different infections, in individuals with a predisposition for it. The close association of E. N. with tuberculosis has been demonstrated by ERNBERG's (12) (1921) and WALLGREN's (13) (1926—1940) investigations on children. In WALLGREN's group of examined children (1937) (14), tuberculous etiology was ascertained in 95 per cent of the cases. The remaining 5 per cent appeared in connection with various infections, especially pharyngitis and tonsillitis. English and American authors (COLLIS (15) (1931—33—35) and others) give considerably higher figures (up to 30 per cent) for E. N. of non-tuberculous character, attributing its causation in such cases chiefly to hemolytic streptococci. As hemolytic streptococci are very often found in rheumatic infec-

tions, this form of E. N. has been termed in Anglo-Saxon countries »rheumatic».

LÖFGREN (16) (1945), having made systematic studies of an E. N. material comprising nearly 200 adult cases from St. Göran's Hospital in Stockholm, has arranged these cases in the following etiologial groups:

Tuberculosis (active, 44 %) . . . . .	58.4 %
Streptococcal infections . . . . .	16.9 %
Bilat. hilus lymphoma with slight or neg. tuberculin reaction .	5.6 %
Lymphogranulomatosis benigna . . . . .	3.4 %
Uncertain cases (whereof 1.7 % with non-specific Wassermann)	15.7 %

After the discovery of sulfatiazol, and with the steadily increasing use of this compound, observations of E. N. complications chiefly in adults have been reported by various authors. In Sweden: BERGLUND & FRISK (17), LÖFGREN (18); in Switzerland: GSELL (19), MIESCHER (20); in Denmark: JERSILD & IVERSEN (21); in America: LONG, HAVILAND, BLISS & EDWARDS (22); DOWLING & LEPPER (23), VOLINI, LEWITT & O'NEIL (24), CAREY (25) and others.

As regards the occurrence of this so-called sulfatiazol-E. N. in adults, it has been found, according to the hitherto published reports, that it manifests itself mainly under the same conditions, and in association with the same diseases, as the ordinary type of E. N., thus most frequently in tuberculosis and diseases caused by streptococci.

In BERGLUND & FRISK's (1941) adult material, E. N. occurred more frequently in association with streptococcal than pneumococcal pneumonia. In GSELL's (1940) adult material it was usually found in association with tonsillitis and polyarthrits, diseases which are often caused by hemolytic streptococci.

CAREY's (1940) study is concerned with E. N. in children, but he gives no detailed description of his material. JERSILD & IVERSEN (1942) were the first to broach the question of a connection between tuberculosis and sulfatiazol-E. N. Their material comprised children as well as adults, most of whom were suffering from pneumonia (52 %) or scarlatina (38 %). Seven patients, of whom four were children (1 pneumonia and 3

scarlatina), contracted Erythema Nodosum. Six of them were tuberculin-negative. The seventh, a 68-year-old patient with bronchopneumonia was tuberculin-positive for 0.01 mg. In three of these seven cases the patients had received sulfatiazol a short time before. Six of these cases were carefully examined 4—8 months later without finding any signs of tuberculosis.

Also LÖFGREN (1944—45) has studied sulfatiazol-E. N. with regard to tuberculous infection.

In his material (1945) 25 patients had received sulfa treatment, 21 of them sulfatiazol. The etiology was active tuberculosis in about half the number of cases; in one-third hemolytic streptococci with a slight sensitivity to tuberculin were observed. The remaining cases were likewise faintly tuberculin-positive, but otherwise of obscure genesis. LÖFGREN considers that E. N. often occurs as a summation phenomenon between an infectious disease with a fever course and a precipitating non-specific factor such as tuberculin, Frei-antigen, sulfatiazol, acute catarrhal infection etc.

MIESCHER (1943), in his study, has thoroughly discussed the cibazol-(i. e. sulfatiazol)-E. N. His material is taken from the pediatric and dermatological clinics in Zürich. The group of examined children consisted of 361 cases of different infectious diseases. E. N. had occurred in the following percentages:

3.6	in association with	pneumonia	. . . .	(116 cases)
8.6	»	»	»	scarlatina . . . . 58 »
15	»	»	»	meningitis . . . . 26 »
0	»	»	»	poliomyelitis . . . 112 »

In the sulfatiazol-treated material of over a thousand cases from the dermatological clinic, E. N. had occurred merely in one. MIESCHER tells us nothing about the tuberculin sensitivity in these cases.

Investigators had previously been inclined to regard sulfatiazol-E. N. as analogous with the ordinary medicinal exanthemata, but in course of time have come to view it as an exanthema *sui generis*. MIESCHER draws attention to several circumstances which, besides its appearance and localization, distinguishes it from undoubted

medicinal exanthemata. In the latter the exanthema is usually exacerbated by continued medication, whereas in MIESCHER's experience of sulfatiazol exanthema, it disappeared in more than half the cases despite the continuance of the medication. Moreover, relapses of the exanthema were usually observed if the same drug was given one or more times after the exanthema had faded. In sulfatiazol exanthema this happened in merely one-fourth of the cases, and in all but one of them the patient had retained his basic infection, or there had been a relapse of the latter. The group specificity often occurring in ordinary drug exanthema is missing. If E.N. complications have been induced by the sulfatiazol medication and if that compound is replaced by another sulfacompound, the E.N. efflorescences almost always disappear.

There are indeed some reports regarding E.N. in connection with sulfonamid, sulfadimin and salazopyrin therapy, but in comparison with those regarding sulfatiazol-E.N. they are extremely few.

LOVERMANN and SIMON (26) (1940) have published one, LÖFGREN (1944) two cases after sulfonamid treatment, the last-mentioned author moreover one after the administration of salazopyrin a chemical compound of salicylic acid and sulfapyridin.

The exanthemata occurring in connection with the other sulfacompounds are usually scarlatiniform, morbilliform or urticarial. It should be added, however, that the exanthema of this type has been observed also in sulfatiazol medication.

According to MIESCHER, medicinal exanthemata are also usually independent of the disease in question, whereas the sulfatiazol exanthema usually appears in association with special diseases, particularly, as previously mentioned, in connection with tuberculosis and streptococcal infections.

MIESCHER, moreover, histologically examined sulfatiazol-E.N. and grouped them into two types: one deep and one superficial, the former of which is found in four-fifths of the cases. The deep E.N.-type, according to the same author, shows, a typical picture with granulation knots and leukocytes, whilst the superficial type mostly resembles a septic skin metastasis with

preponderant leukocyte infiltration. As compared with the maculopapular medicinal exanthemata, considerable differences are observed, especially the lack of granuloma formations and the abundant occurrence of lymphocytes, whereas the leukocytes occur only sparsely.

If, again, the histological picture in sulfatiazol-E. N. is compared with ordinary E. N. (both tuberculin-positive and -negative), as the latter has been described by WALLGREN and GNOSSELIUS (27) (1940), one will find, as regard the deep type, almost identical pictures.

In view of the complicated histological picture with granuloma knots and giant cells, MIESCHER doubts whether these complicated structures could arise during the brief interval between the administration of the sulfatiazol and the manifestation of Erythema Nodosum. He supposes that granulomatous, clinically not observable, formations lie in the subcutis, and that, when the sulfatiazol is administered, these formations are activated and manifest themselves as Erythema Nodosum. The sulfatiazol apparently acts as a catalyzer for these formations. Or else through the action of the sulfatiazol, a number of bacterial products flow out into the blood and give rise to the allergic reaction.

MIESCHER tested several of his cases for cutaneous sensitivity to sulfatiazol without obtaining a positive result in any single instance. LÖFGREN (1944) had the same experience. MIESCHER made further cutaneous tests with streptococcal and staphylococcal toxins, mixtures of sulfatiazol and bacterial filtrates as well as with specially prepared bacterial products of streptococci and staphylococci, but the few positive results do not permit any definite conclusions. The material tested was quite small. MIESCHER considers that eibazol-(sulfatiazol) exanthema is caused by allergic and toxic bacterial products which are generated or activated by the sulfatiazol.

It appears from the above that a number of investigations regarding the E. N.-eruption in connection with sulfatiazol therapy have been made, but they have mainly been concerned with adults. As studies made with special regard to E. N. in tuberculin-positive children in connection with sulfatiazol treatment had

not been found in the literature, the author examined the material at the pediatric clinic of the Norrtull Hospital.

On the basis of the experience gained from this material of 15 cases, an investigation, of which the present work is merely a part, was started. The object is to ascertain whether from these E. N.-eruptions occurring in connection with sulfatiazol any conclusions can be drawn regarding the precipitating mechanism for Erythema Nodosum.

The problems to be studied were the following:

I. In cases of primary tuberculosis in children does E. N. occur oftener after sulfatiazol treatment than without it?

II. Does sulfatiazol, given during the fever stage in primary tuberculosis in children, provoke E. N. more often than in fevers induced by some other cause?

III. Has the precipitating mechanism for E. N. in tuberculosis in connection with sulfatiazol treatment anything to do with the age of the process?

IV. Is there any difference in the precipitating mechanism for E. N. in cases with fever and cases without fever?

V. What part is played by mixed infections and the hemolytic streptococci for the precipitating mechanism of E. N.?

VI. Does sulfatiazol-E. N. appear after a certain interval? Does sensibilization against sulfatiazol occur?

VII. Is E. N. provoked by sulfatiazol, morphologically and clinically distinct from »ordinary» E. N.?

VIII. Can sulfatiazol-E. N. be diagnostically utilized in view of tuberculous infection?

The investigation at the Norrtull Hospital comprises all the cases of E. N. as from the year 1942. Up to the end of 1944, 90 cases of E. N., of which 75 were tuberculin-positive and 15 tuberculin-negative, have been treated during three years.

The results of the entire investigation will be published later. This report includes merely the tuberculin-positive cases which in 1944 had been treated with sulfatiazol in order to ascertain under what conditions E. N. can be provoked. These cases were not examined for the occurrence of hemolytic streptococci. An investigation of that nature is, however, proceeding at present.



Table 1. Cases of primary tuber-

No.	Sex	Age years	Probable age of Tbc-process in months	Simultaneous acute infections	Earlier sulfa- treatment	Sulfatiazol	
						Total dose gr	in days
1	♂	8½	½, Max. 2½	Pharyngitis ac.	0	9	2
2	♂	6	Unknown	» levis	?	16.5	4
3	♂	4	3½	Pneumonia+Abscess	0	8.9	3
4	♂	1½	½	Pharyngitis ac.	P immed. before	3.75	3
5	♂	1	<1	0	P 1 month before	4	3
6	♂	4	? Not recent	Pharyngitis ac.	?	7	3
7	♂	4	? Not recent	Angina tons. Otit. ac.	?	11.6	6
8	♂	3½	<1½	0	0	3.15	2
9	♂	2½	? Not recent	Pharyngitis ac.	?	6.3	4
10	♂	3½	1½—3	» »	0	6.7	3
11	♂	3½	2	» »	0	5.3	3
12	♀	4½	Old (24)	Otitis chron.	?	4.3	3
13	♀	1½	<4	Pharyngitis ac.	0	5	3
14	♀	2	½	Tonsillitis ac.	0	4.5	1
15	♀	8½	Old	0	?	10	3½
16	♂	2	>3	0	0	5.7	3
17	♂	4½	Old (24)	Pharyngitis levis	?	7	3
18	♂	10½	? Not recent	Tonsillitis ac.	?	9	2
19	♀	11½	Old (40)	Bronchopneum. ac.	Sulfonamid 1942	29	4
20	♀	2½	? Not recent	0	0	7.5	3
21	♂	8/12	<½	Pharyngitis levis	Z one month before	4.5	3
22	♂	3	½	» »	0	8.1	3
23	♂	1 9/12	<2	» ac.	?	4.5	2
24	♀	7½	½	» »	M&B 39, Z and Di- min 44	13.5	3
25	♂	1½	Max. 2	» »	0	2.7	2
26	♀	12	½	» levis	?	8.1	3
27	♂	8	Max. 12	Bronchopneum. ac.	0	25.5	8
28	♂	1	7—8	Pharyngitis ac.	P one month before	5	3
29	♂	4	<2	0	0	5.6	3
30	♀	2½	½—2	Pharyngitis ac.	0	6.8	3
31	♂	10/12	Max. 2	» »	0	5	3
32	♂	8	>12	» »	?	8.4	3
33	♀	4½	? Not recent	Pharyngit. Otit. ac.	P?	7	3

Abbreviations: Dimin = Sulfapyrimidin, P = Sulfapyridin, Z = Sulfatiazol, fatiazol-treatment without E. N.-provocation.

culousis treated with sulfatiazol.

Max. temp. and temp. trend during sulfatiazol-treatment	E. N.	Interval sulfatiazol—E. N. in days	Subsequent sulfatreatment and eruption of E. N.	Notes
39° Unaffected	+	1	0	Pleurit?
40 Falling	—		0	Meningitis
High, septic	+	3	0	E. N. 1943
39 Unaffected	+	2	Z E. N. Z 0	
39 »	—		0	Miliaris
39 Falling	—		0	Refugee
40 »	—		0	»
37.5	—		Z E. N.	Meningitis
38.5 Falling	—		0	Refugee
37.8	—		0	»
37.4	+	3	0	E. N. 1944
37	—		0	Refugee
37	—		0	
38.5 Unaffected	—		Z E. N. Z 0	
37	—		0	Refugee
37.6	—		0	
39.2 Falling	—		0	E. N. 1942
37.7	—		0	
39.2 Unaffected	—		Z E. N.	E. N. 1940
37	—		0	
37.6	—		0	
38.9 Unaffected	+	4—6	0	
39.4 First down, then up	—		P 0	Miliaris, Refugee
38 Rising	+	2	0	
37.2	—		0	Z discontinued because of vomiting
37.9	+	2	0	Refugee
39.5 Falling	—		0	
38.6 Falling	—		Z 0 Z 0	
37.7	+	3	0	
38.7 Falling	+	3	0	
37.7	—		0	
37.8	—		0	Refugee
37	—		0	

E. N. = E. N.-provocation in connection with sulfatiazol-treatment, Z 0 = Sul-

A trial excision of the E. N. efflorescences was not made, as by the above-mentioned investigations (JERSILD & IVERSEN, 1942, MIESCHER, 1943, and LÖFGREN, 1944) the anatomical structure of the sulfatiazol-E. N. may be considered to have been ascertained.

The provocation cases are 33 in number and consist of children with tuberculous infection, aged 8 months to 11 years (Table 1). The diagnoses were made by tuberculin tests and roentgen. The cases were not specially selected. With a few exceptions all the cases of tuberculosis during the last nine months of 1944 were tested in the same way. At first sulfatiazol was administered only to patients with fever, but afterwards also to those with a normal temperature. As sulfatiazol-E. N. usually manifests itself within three days (LÖFGREN (1944), the author's own experiences in 83 % of the cases), the sulfatiazol was given for three days and in an ordinary pneumonia dosage, reckoned according to 0.05 g per kg body-weight, as two initial doses and afterwards half that dose every fourth hour. In the table only the total doses have been included.

The sulfatiazol was discontinued as soon as E. N. had manifested itself, or if the patients had shown, for example by vomiting, that they could not tolerate the treatment. This occurred in three cases. Two of them were meningites, whence the cause of the vomiting need not necessarily be attributed to the sulfatiazol. Generally speaking, children stand sulfatiazol much better than adults. In a few cases sulfatiazol was administered two or three times with intervals of different lengths and under different conditions, in order to ascertain whether the temperature or the infection may in some way have affected the provocation mechanism.

In judging the age of the tuberculous process, reckoned as from the appearance of the allergy after the end of the incubation time, difficulties naturally arose. In some cases it was without doubt merely a few days old, as a tuberculin test on the days before the onset of the fever had been negative and afterwards became positive. In other cases it was estimated on the basis of previous negative tuberculin tests, the condition of the patient after that test (fever states, catarrhalia, etc.) up to the occasion when he had been found tuberculin-positive. If the patient during

the intervening period had been in good condition without any fever, the fever during which tuberculosis had been detected — provided that the roentgen finding had corresponded to a fresh epituberculous infiltrate —, was considered to be an initial fever, and the age of the process was thus reckoned from the first day of its appearance. Regard was also paid to the time of exposure to the tuberculous infection, and the sedimentation reaction (S. R.) was taken into account. Cases where it had been reduced to the normal within a short space of time after the fall of temperature and where the roentgen finding had shown earlier fibrous foci were viewed, with due regard to other circumstances, as not recent processes.

The temperature conditions are indicated in the table, firstly the maximum temperature during the sulfatiazol treatment and secondly the temperature during the medication. So far as possible, it was ascertained whether the patients had received sulfa-treatment before. In several cases, where the children were refugees from Finland, Norway and Estonia, this was found impossible. The E. N. column only shows the result of the *first* sulfatiazol medication. If sulfatiazol was given a second time or more, this is indicated in a separate column.

#### *Discussion of the Cases.*

The material comprised 23 boys and 10 girls. Among the older patients affected with E. N., the women always predominate. In children, however, we do not find this marked sexual predilection. In the author's total material of 90 cases, it is noteworthy that 53 were boys and 37 girls. In LEVIN's (28) material (1929) the figures for 168 cases were 73 boys and 95 girls, those of KOCH (29) (1926) 20 boys and 28 girls.

The number of cases in the authors different age-groups is as follows: 1—3 years 14, 3—6 years 11, 6—9 years 5, 9—11 years 3.

In the author's entire E. N. material there was no case of that disease in babies. The youngest case was one and a half years old. »A rule without known exceptions is that tuberculous babies never get E. N. during their 'invasion fever'» (WALLGREN (30), (1926).

The cases were divided into three groups. The basis of this division is the fact that practically all the »ordinary» E. N.-eruptions in tuberculin-positive cases occur at the onset of allergy. The cases of E. N. which occur at a later stage are comparatively rare and depend on factors which affect the allergy, such as injections of tuberculin, infections such as morbilli, scarlatina, etc.

Group I (Table 2) comprises patients with initial fever. Group III (Table 4) comprises firstly fresh cases where the initial fever stage has been passed, and secondly older cases of primary tuberculosis of the lungs. Group II (Table 3) comprises uncertain cases holding an intermediate position between groups I and III. It consists of cases where it could not be decided with certainty whether the existing rise of temperature was due to the allergic change, to complications (miliaris, meningitis) or to a simultaneous catarrhal infection.

*Group I. Primary tuberculosis cases treated with sulfatiazol during the initial fever stage.*

Table 2.

Group I. Cases of primary tuberculosis, treated with sulfatiazol during initial fever stage.

No.	Simultaneous acute infection	Earlier sulfatreatment	Max. temp. and temp. trend during sulfatiazol treatment	E. N.	Subsequent sulfatreatment and any cases of E. N.
4	Pharyngit. ac.	P	39 Unaffected	+	Z E. N. Z 0
14	Tonsillitis »	0	38.5 »	—	Z E. N. Z 0
22	Pharyngit. levis	0	38.9 »	+	0
24	» ac.	M & B 1939 Z and Dimin 1944	38 Rising	+	0
26	» levis	?	37.9 —	+	0

Abbreviations: P = Sulfapyridin, Dimin = Sulfapyrimidin, Z E. N. = E. N.-provocation in connection with sulfatiazol-treatment, Z 0 = Sulfatiazol-treatment without E. N.-provocation.

This group comprises five cases, three girls and two boys aged 1 <sup>1</sup>/<sub>2</sub>—12 years. All of them had catarrhal infections: one

tonsillitis, the others pharyngites of different intensity. Three cases of them had not previously received sulfa-treatment. In two of the cases sulfamedication had been given before, in only one of them sulfatiazol, whence the sensibilization effect must be taken into account here. As this patient was nursed only for a short time at the hospital, there was no time for any further sulfatiazol testing. In one case it was impossible to ascertain whether sulfamedication had been given previously. According to HELLERSTRÖM (31), one must reckon in sulfamedication per os with a sensibilization effect of 3—10 %, but also higher figures are given. (Cited HELLERSTRÖM, 1944.) In three of the cases initial fever over 38° C occurred, in the others about 38°. In all the cases where fever was found, the sulfatiazol did not have any fever-reducing effect. Four of these five patients had developed E. N. in connection with the first sulfatiazol treatment. The remaining case, No. 14, who had not had E. N. at his first treatment, reacted with E. N. a week later. This case merits a closer examination.

It is a case of a two-year-old girl who had previously, generally speaking, been healthy. In the autumn of 1943 she was tuberculin-negative. On the 25th September 1944 she had a cold, cough and a fever of about 38—39°. Arrived at the hospital on the 28th September, showing tonsillitis, conjunctivitis and a temperature of 38.5. The respiratory sound weakened in the right lung. Received sulfatiazol for three days without any noticeable effect. On the fourth day the temperature fell to 37.5, whereupon the sulfatiazol was discontinued. The little patient had then received 4½ gr of sulfatiazol. No skin complication. On the 2nd October the percutaneous tuberculin test was positive; the patient was therefore x-rayed and was found to have a right-sided hilus process. Sedimentation Rate 58. After having been fever-free for one day, she suddenly and quite inexplicably had a fever peak of 40.3°. The tonsillitis was clearing. Ears nothing noteworthy. Sulfatiazol was now given for testing purposes in the same dosage as before. On the following day the little girl had typical E. N. on arms and legs. The temperature fell within 24 hours, so that the sulfatiazol was discontinued. She had then received 2 gr of that drug. E. N. paled after 48 hours. On the 15th of October, as the patient had been free from fever for 9 days and entirely free from catarrhal infection, sulfatiazol was given again for 3 days, about 4.75 gr, without any manifestation of E. N.

Summing up, this was a case of a little girl who had received sulfatiazol three times under different conditions during the first 20 days of her primary tuberculosis. On the first occasion she had tonsillitis with a fever of about  $38.5^{\circ}$ , which was not reduced. She had no Erythema Nodosum. A week later when the tonsillitis was clearing, she had a quite inexplicable fever peak and, having received sulfatiazol again, now reacted with E. N. The last time she was tested she was free from catarrhal infection and fever and did not react with E. N.

We might be inclined to explain the E. N.-eruption after the second sulfatiazol medication as a sensibilization effect, but the result of the third treatment rules out this supposition. Unfortunately no examination was made for hemolytic streptococci, but it is scarcely probable that the patient would have been thus affected in connection with the second administration of sulfatiazol, especially as she was treated in a separate room. Had this been the case, the tonsillitis, one would think, ought to have been aggravated, instead of paling.

Case No. 4 also deserves further examination.

It is a case of a  $1\frac{1}{2}$ -year-old boy, who had previously been sturdy and healthy. Exposure to tuberculous infection not known. Admitted to the hospital on the 24th April 1944 because of a slight pharyngitis and high fever since the 15th April. As the temperature did not fall, a private practitioner administered sulfapyridin, of which the little patient received  $4\frac{1}{2}$  tablets for some days. The fever then subsided and the tablets were discontinued. The next day fever of  $39^{\circ}$ , which was maintained till admission on the 24th. On examination only pharyngitis was found. S. R. 40. Sulfatiazol was administered on the 24th—26th (total dose 3.75 gr) without affecting the fever. On the 26th typical E. N., which remained till the first few days in May, were observed on the lower legs. The tuberculin reaction, which during the first few days had been negative up to 1 mg, was found on the 2nd May, on renewed testing with percutaneous tuberculin, to have become positive. Roentgen examination on the 26th April had revealed a right-sided hilus enlargement, which was at first regarded as non-specific, in view of the negative reaction to tuberculin. Three weeks later (on the 14th May) the temperature, which had been normal, rose to about  $38-39^{\circ}$ , with signs of asthmatic bronchitis. Sulfatiazol was administered as before without affecting the temperature. After the lapse of about 48 hours there was new eruption of E. N., but considerably larger than on the

previous occasion. The nodules paled within 48 hours. On the 25th May sulfatiazol in the same dosage was administered for the third time, when the patient had a normal temperature and showed no signs of catarrhal infection. On this occasion he did not react with E. N.

Summing up, this was a case of a 1½-year-old boy, who during the first month of his primary tuberculosis received sulfatiazol three times. On the first two occasions he had a catarrhal infection and a fever of about 38°, which was not affected by the sulfatiazol, and reacted on both occasions with E. N. within 48 hours. On the third occasion, when he was free from catarrhal infection and fever, he had no eruption of E. N.

Both these cases showed one feature in common, namely that E. N. could not be provoked where there was no catarrhal infection and no fever. They give one the impression that the catarrhal infection and the fever which attended it had a determining effect on the mechanism which precipitates E. N. Whether the throat infection had been induced by hemolytic streptococci was not ascertained. No definite conclusions can be drawn from these few cases. It is, however, very noteworthy that all the cases tested with sulfatiazol during recent primary tuberculosis with initial fever reacted with erythema nodosum.

*Group II. Sulfatiazol-treated recent cases of primary tuberculosis with fever of obscure genesis. (Table 3.)*

This group comprises 6 cases, 5 boys and 1 girl of the ages 1—8 years. The rise of temperature which was found in all cases (in two of them merely subfebrile) could not be diagnosed with certainty as initial fever. Four of the cases were complicated, two with miliaris, one with meningitis and one with suspected pleuritis. E. N. was provoked in four cases, but in one of them, number 8, not to the second sulfatiazol treatment.

*Case No. 1* relates to a boy aged 8½, who on the 25th November 1943 was tuberculin-negative and did not show any pathological changes on the screen-photograph. At the end of January 1944 he became listless. He had diarrhea and fever of about 39°. X-ray-examination of the lungs showed on the 4th February large right-sided hilus changes and a very small pleural exsudate. As the fever reappeared some days later he was admitted on the 8th February and had then a temperature of



Table 3.

Group II. Sulfatiazol-treated recent cases of primary tuberculosis, with fever of obscure genesis.

No.	Probable age of The process in months	Simultaneous acute infection	Earlier sulfa-treatment	Max. temp. and temp. trend during sulfatiazol-treatment	E.N.	Subsequent sulfa-treatment and any cases of E. N.	Notes
1	$\frac{1}{2}$ ? Max. $2\frac{1}{2}$	Pharyng. ac.	0	39 Unaffected	+	0	Pleurit?
5	<1	0	P 1 month before	39 »	—	0	Miliaris
8	<1 $\frac{1}{2}$	0	0	37.5 —	—	Z E. N.	Meningit.
23	<2	Pharyng. ac.	?	39.4 First down, then up	—	P 0	Miliaris
29	<2	0	0	37.7 —	+	0	—
30	<2	Pharyng. ac.	0	38.7 Falling	+	0	—

Abbreviations: P = Sulfapyridin, Z E. N. = E. N.-provocation in connection with sulfatiazol-treatment, Z 0 = Sulfatiazol-treatment without E. N.-provocation.

about 39° and pharyngitis. The cutaneous tuberculin test positive on the 11th February. Received sulfatiazol for testing purposes and reacted on the following day with E. N. The fever was not reduced by the sulfatiazol. It remained between 38 and 39° for about at fortnight. The x-ray-examination did not show any progress of the suspected pleuritis.

Though it is thus a case of a very recent process, it has been included in this group in view of the roentgen finding. If a genuin pleuritis really existed, the fever was presumably due to it. The pleuritis complication, however, usually comes much later in the course of the disease than in this case, where the tuberculous process was at most  $2\frac{1}{2}$  months old. Moreover, during the time which had elapsed between the two tuberculin tests and in which the allergic change must have taken place, the patient had not had any fever or looked ill until now, for which reason it may be considered that it was a case of initial fever.

*Case No. 5* relates to a one-year-old boy who was treated at the hospital at the end of March 1944 for a rhino-pharyngitis. The tuberculin test was negative. Roentgen examination of the lungs showed nothing noteworthy. A fortnight later the patient was remitted to the hospital for infectious diseases because of morbilli, where he lay in high fever when the exanthema had paled. Received sulfapyridin without effect on the fever. Roentgen examination of the lungs on the 27th April showed right-sided hilus lesions, and the patient was therefore sent back to Norrtull Hospital. The tuberculin tests now positive. Received sulfatiazol for testing purposes for three days, without effect on the fever. Did not react with E. N. Roentgen examination on the 12th May showed miliaris. The patient died 3 weeks later.

*Case No. 8* relates to 3½ year old boy, who had previously been healthy. On the 3rd May 1944 listless, tired and sleepy. Temperature about 39°. On the 9th May he was found to be tuberculin-positive and was therefore admitted to the hospital on the 15th May. Was then sub-febrile and had pharyngitis. Roentgen examination of the lungs showed a right-sided primary complex. The temperature, which had been almost normal for a few days, gradually rose. X-ray showed advance of the lung process. On the 30th May sulfatiazol was administered for testing purposes, at a temperature of 37.5 and with signs of inflammation of the throat. As the temperature was rising and »drug fever» was suspected, the sulfatiazol was discontinued on the second day. No E. N. Afterwards symptoms of meningitis and rising temperature. On the 10th June sulfatiazol was again administered for 3 days for testing purposes, at a temperature of about 39°. The temperature was not affected. After 2 days three E. N. about the size of a pea, but quite typical, developed; they rapidly cleared when the sulfatiazol had been discontinued.

*Case No. 23* relates to an Estonian refugee boy, one year and nine months old. The anamnestic data uncertain. Is said to have had diarrhea in August, and both in October and November a fever period of about 14 days in connection with catarrhalia. According to an unconfirmed statement, a roentgen examination of the lungs on the 28th November showed nothing pathological. During the first days in December he had a stiff neck and diarrhea. Was admitted on the 2nd December. The temperature over 39°. Lumbar puncture showed meningitis and the x-ray examination of the lungs revealed hilus changes and miliaris. The tuberculin test gave no definite result. Received sulfatiazol for 2 days, after which it was discontinued on account of vomiting. The temperature fell at first, but then again rose. Died on the 8th December.

In regard to these three cases Nos. 5, 8 and 23 it cannot be determined with certainty, whether the rise in temperature was

due solely to the complication, or whether the initial fever stage had directly passed into or coincided with the fever which accompanies these pleural, meningal and miliaris complications.

*Case No. 29* relates to a four-year-old boy who had previously been healthy. Since the 7th November tired and had a temperature of about 38.5. Pirquet positive on the 9th December and then subfebrile. Admitted on the 21st December, when he had a normal temperature and no signs of catarrhal infection. Received sulfatiazol for three days and reacted on the third day with E. N. The temperature had again become subfebrile. The roentgen examination showed a left-sided primary complex.

As the patient had been entirely feverless for some days before the sulfatiazol treatment, but during that treatment had a slight rise of temperature which may possibly be interpreted as the last manifestations of the initial fever, the case was included in this group.

*Case No. 30* relates to a 2  $\frac{1}{2}$  year old girl, who, generally speaking had previously been healthy. Tuberculin-negative on the 28th October. Tuberculosis having been detected in her mother in November, a new tuberculin test was made on the 20th December, this time with a positive result. The girl during the intervening time had been apparently quite well. Roentgen-examination on the 23rd December showed right-sided hilus lesions. Was admitted on the 29th December. Had then a temperature of 38.7° and pharyngitis. Sulfatiazol was administered, whereupon the temperature fell. On the third day she reacted with E. N.

This case is obscure. The patient had been tuberculin-tested 7 weeks before admission and had been found negative. Afterwards apparently healthy until admission, when she had an infection of the throat and a fever of over 38.5°. In ordinary cases this rise of temperature would have been regarded as initial fever, had it not been for the result of the sulfatiazol treatment. In all the other certain cases of initial fever the sulfatiazol treatment had no fever-reducing effect; in this case the temperature fell.

Out of the four E. N. eruptions within this group, three occurred in connection with the first sulfatiazol treatment. Two of these cases had at the same time an infection of the throat, the third was not catarrhal. None of these patients had had sulfatreatment before. In one of the cases the fever was completely

unaffected, in one it fell in connection with the treatment, and in the third the patient showed a slight rise of temperature in connection with the sulfatiazol. The fourth E. N.-eruption (case No. 8) did not occur to the second sulfatiazol treatment. The interval between the two treatment was 8 days, so that a sensibilization effect cannot be ruled out.

In the author's total material of primary tuberculosis cases there are 6 cases of meningitis and miliaris. One cannot, of course, draw any conclusions from these few cases, but it seems remarkable that in none of them was E. N. provoked at the first sulfatiazol treatment. Do meningitic and miliary complications perhaps involve some check on the mechanism which precipitates E. N.?

*Group III. Cases of primary tuberculosis treated with sulfatiazol after initial fever stage, and earlier primary processes, treated with sulfatiazol.*

This group comprises 22 cases of primary tuberculosis of the lungs in children aged  $\frac{8}{12}$ —11 years, of which 16 were boys and 6 girls. The age of the tuberculous process varies from quite recent cases to older cases over 2 years. In the recent cases the initial fever stage had been passed.

In the cases where the patients had had fever during the sulfatiazol treatment it was due, so far as could be judged, to some other infection or complication. In 7 cases the fever was induced by catarrhal infection. In 5 of them, where the patient had tonsillitis or pharyngitis, and in one, where the patient had broncho-pneumonia, the fever was normally reduced by the sulfatiazol. In 2 cases it was unaffected. One of them, No. 3, in addition to the tuberculous lung process, had pneumonia with liquefactions which were considered to be caused by the latter disease. The other case, No. 19, had broncho-pneumonias, (the tuberculosis process was of long standing). One case had meningitis.

In three of the cases sulfa-compound had been given earlier, but in none of them had the patient reacted with E. N. at the first sulfatiazol treatment. In nine cases where the patients were refugee children, it could not be ascertained whether previous

Table 4.

Group III. Cases of primary tuberculosis, treated with sulfatiazol after initial fever stage, and old primary processes, treated with sulfatiazol.

No.	Probable age of Tbc-process in months	Simultaneous acute infection	Earlier sulfatreatment	Max. temp. and temp. trend during sulfatiazol-treatment	E.N.	Subsequent sulfatreatment and any cases of E. N.	Notes
2	Unknown	Pharyng. levis	?	40 Falling	—	0	Meningit.
3	3½	Pneum. + Abscess	0	High, septic	+	0	E. N. 1943
6	Not recent	Pharyng. ac.	?	39 Falling	—	0	
7	» »	Tonsill. Otit. ac.	?	40 »	—	0	
9	» »	Pharyng. ac.	?	38.5 »	—	0	
10	1½—3	» »	0	37.3 —	—	0	
11	<2	» »	0	37.4 —	+	0	E. N. 1944
12	Old 24	Otitis chron.	?	37 —	—	0	
13	<4	Pharyng. ac.	0	37 —	—	0	
15	Old 0	0	?	37 —	—	0	
16	>3	0	0	37.6 —	—	0	
17	Old 24	Pharyng. levis	?	39.2 Falling	—	0	E. N. 1942
18	Not recent	Tonsillitis ac.	?	37.7 —	—	0	
19	Old 40	Bronchopneum.	S 1942	39.2 Unaffected	—	Z E. N.	E. N. 1940
20	? Not recent	0	0	37 —	—	0	
21	<½	Pharyng. levis	Z 1 month before	37.6 —	—	0	
25	Max. 2	» ac.	0	37.2 —	—	0	
27	Max. 12	Bronchopneum.	0	39.5 Falling	—	0	
28	7—8	Pharyng. ac.	P 1 month before	38.6 »	—	Z 0 Z 0	
31	Max. 2	» »	0	37.7 —	—	0	
32	>12	» »	?	37.8 —	—	0	
33	? Not recent	» Otit.	0	37 —	—	0	

Abbreviations: P = Sulfapyridin, S = Sulfonamid, Z = Sulfatiazol, Z E. N. = E. N.-provocation after sulfatiazol-treatment, Z 0 = Sulfatiazol-treatment without E. N.-provocation.

sulfa-medication had been received, but none of them had E. N. In one of the cases which reacted with E. N. the patient in 1942 had received sulfonamid, but in this particular case the reaction did not occur until the second sulfatiazol treatment. In the two remaining cases, where the provocation of E. N. succeeded, it was ascertained that sulfa-medication had not been given previously. Thus in this group the whole question of sensibilization effect at the first sulfatiazol treatment is eliminated.

Altogether, E. N. was provoked in 3 cases; Nos. 3, 11 and 19. Out of these, two, Nos. 3 and 11, came at the first sulfatiazol treatment and the other, No. 19, at the second. All of them had had E. N. previously. In the two cases where the provocation succeeded the first time, the interval from the previous spontaneous E. N. eruption was short: 2—3 months. In the third case, where E. N. did not manifest itself until the second treatment, the patient had had the first E. N. somewhat more than 3 years before.

The temperature conditions varied in these three cases. In one of them high septic fever, in one subfebrile and in the third no fever. In this last case, however, the patients showed signs of throat infection.

The result of the sulfatiazol testing in group III was, that out of 22 treated cases E. N. was provoked in three. All these patients had had E. N. before, at the commencement of the primary tuberculosis. One of these cases, however, did not react until the second sulfatiazol treatment, whence we cannot explain E. N. solely as a relapse, but must take the sensibilization effect into account.

Since we know that ordinary E. N., as above mentioned, recurs in connection with factors which affect the allergy, these relapses of E. N. in connection with the sulfatiazol medication are quite explicable. The sulfatiazol apparently acts as a catalyzer on structures which have long lain in the subcutis. In MIESCHER's material there was no relapse of E. N. in three-fourth of the cases. Case No. 17 who had previously had E. N., may be classed among them. In this case, however, the tuberculin sensitivity was marked. Positive reaction to Mantoux 0.001 mg.

The administration of sulfatiazol, however, was continued only for two days, which is a shorter time than in the other cases. Moreover, the patient was being treated for eczema, which may have had a bearing on the reaction of the skin.

Now how can these »relapses» of E. N. be explained? In two of the cases the interval from the preceding E. N. eruptions was relatively short, and the tubercular process was still active. We can therefore very well conceive that latent hypothetic granuloma formations remain in the subcutis after the previous efflorescences had clinically cleared. In these cases it is conceivable that we are concerned with a genuine relapse. In the third case, where E. N. did not manifest itself until the second sulfatiazol treatment, a similar explanation would be farfetched. It is conceivable that these granuloma formations lying in the skin in cases of E. N. may long remain latent, like certain tuberculous changes in the lungs. The latter can be activated a long time afterwards by factors which affect the allergy. In this case the sulfatiazol would be the factor affecting the allergy.

This theory could easily be tested. All that is necessary would be to reliably localize the sites of some E. N. efflorescences and then after intervals of different lengths, make a trial excision. As regards patients who had died, a systematic investigation of the sites of predilection of E. N. could be made. A more probable explanation of this E. N. »relaps» would be that the E. N. eruption is a summation product of the predisposition to E. N. and of sensitivity to the sulfatiazol.

#### *Conclusions.*

If we compare the experiences from these three groups of altogether 33 cases, it will be found that E. N. was provoked in 12 of them. Out of the latter no less than 9 fall within the two first groups comprising 11 sulfatiazol-treated cases of recent primary tuberculosis. All had shown a rise of temperature which was either a certainly ascertained initial fever (5 E. N. provocations to 5 treated cases), or fever in immediate connection therewith. The remaining 3 cases of E. N. eruption fall within group III, comprising either recent cases of primary tuberculosis,

where the initial fever stage had been passed, or older primary lung processes. All three cases have had E. N. before.

It thus seems as if sulfatiazol could provoke primary E. N. only in recent cases of primary tuberculosis and at the stage of the tuberculous process where the allergic swing-over from tuberculin-negativity to positivity occurs. It is just at this stage that E. N. usually appears. If E. N. is provoked in tuberculous processes of long standing, we must evidently regard it either as a genuine »relapse» or as the effect of sensitivity to sulfatiazol. Nor can the possibility of a new attack of E. N. be ruled out.

A survey of the entire E. N. material of the author's examined hitherto shows the following result:

Out of 170 recent primary tuberculosis cases 75 had E. N. . . . = 42.9 %  
 135 out of these 170 children had not been treated with sulfatiazol,  
 and of them 44 had E. N. . . . . = 34.5 %  
 Out of the remaining 35 cases who had received sulfatiazol treat-  
 ment, 24 had E. N. . . . . = 68.6 %  
 Out of 788 sulfatiazol-treated tuberculin-negative cases, aged 1—15  
 years, who had been treated for some febrile disease, 8 had E. N. = 1.0 %  
 10 children, aged 2—12, who had been treated for mental disorders were  
 given, for the purpose of control, sulfatiazol in the same doses as the  
 tuberculous cases. All of them had been tuberculin-negative to 1 mg  
 and feverless. In none of these cases could E. N. be provoked.

These figures show that Erythema Nodosum in connection with sulfatiazol treatment of a fever in children, with only a few exceptions, is due to fresh tuberculosis infection.

This investigation supports the theory of latent E. N. But what is the part played by the sulfatiazol? By continued studies the author hopes that he may be able to make further contributions to the solution of the problem.

### Summary.

In connection with investigation of the Erythema Nodosum material at the Norrtull Hospital in 1942—1944, the author gave sulfatiazol to children with primary tuberculosis, in order to ascertain under what conditions Erythema Nodosum can be provoked. Out of 33 tested cases of different age with primary tuberculosis of the lungs, Erythema Nodosum was provoked in



twelve, 9 of which were quite recent processes. In all cases where the patients were still in the initial fever stage the provocation succeeded. The remaining three were cases of earlier primary tuberculosis with previous eruption of Erythema Nodosum.

The author arrives at the conclusion that Erythema Nodosum is latent in the subcutis and is provoked by the catalyzation effect of sulfatiazol.

The author finally reports a preliminary result of the investigation of the entire Erythema Nodosum material, showing that practically all cases of that disease in connection with the sulfatiazol treatment of fevers in children occur in association with recent tuberculous infection.

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## Der Arzt und die Sechsjahrmolaren.

Von

BERTIL ROOS.

Die 1. bleibenden Molaren — man pflegt sie auch die 6-Jahrmolaren zu nennen — sind die wichtigsten Zähne des bleibenden Gebisses. Es sind indessen auch diejenigen bleibenden Zähne, die am häufigsten durch Karies zerstört werden. Die Frage ihrer Aufgabe und ihrer Erhaltung hat nicht nur ein speziell odontologisches Interesse. Besonders mit Rücksicht darauf, dass der Arzt die Möglichkeit hat, in gewissen Fällen mit einfachen Mitteln zur Rettung dieser wichtigen Zähne beizutragen, ist es dringend erwünscht, dass der Arzt, der beruflich mit Kindern zu tun hat, über eine Reihe von Fragen betreffs der 6-Jahrmolaren (im folgenden 6-Jm genannt) eingehender unterrichtet ist.

SCHEIDT unterstreicht, dass die 6-Jm die grössten und kräftigsten Zähne im Kiefer sind. Sie befinden sich an der kaufunktionell meist beanspruchten Stelle des Kiefers. Die 6-Jm sind durch eine Kaufläche gekennzeichnet, die von regelmässigerer Form ist als bei irgendwelchen anderen Kauzähnen. Die 6-Jm sind daher geeignet, die Lagebeziehungen der Kiefer und Zähne festzuhalten. Sie werden deshalb von SCHEIDT als die wichtigsten und kaufunktionell tüchtigsten Zähne des ganzen Gebisses bezeichnet. Zu betonen ist in diesem Zusammenhang, dass die 6-Jm von den Milchmolaren die Aufgabe übernehmen, eine richtige Gebisshöhe festzuhalten. Frühzeitiges Schadhafwerden der 6-Jm hat oft Fehlstellungen und Deformitäten des bleibenden Gebisses zur Folge, die ihrerseits ungünstigere Kaumöglichkeiten mit sich bringen und ein kariesförderndes Moment bedeuten.

Die 6-Jm kommen im allgemeinen mit 6 Jahren, nicht selten jedoch mit 5 bzw. 7 Jahren. In vereinzelten Fällen können sie bereits bei Vierjährigen kommen. Nach EKMÄN liegt das Durchschnittsalter bei Durchbruch dieser Zähne bei finnischen Kindern etwas über 6 Jahre, bei den Mädchen etwas früher als bei den Knaben. Der Durchbruch erfolgt auch durchschnittlich im Unterkiefer etwas früher als im Oberkiefer.

Der Verf. hat 1944 die Ergebnisse betreffs der Milchzahnkaries unter einem Material von vorschulpflichtigen Kindern aus Malmö (der grössten Stadt Südschwedens) und den Landbezirken Südwestschonens veröffentlicht. Bei der Einsammlung des Materials wurden Aufzeichnungen über die Anzahl der vorhandenen 6-Jm und den Kariesbefall dieser Zähne gemacht. Das Material kann teils beleuchten, wie viele 6-Jm in den einzelnen Jahresgruppen des Kleinkindesalters durchgebrochen waren, teils wie viele von diesen Zähnen zur Zeit der Untersuchung Kariesbefall zeigten.

Bei der Beurteilung der Anzahl durchgebrochener 6-Jm sind auch solche Zähne als bereits vorhanden gezählt worden, die erst zum Teil die Gingiva durchgebrochen hatten.

*Tabelle 1.*

Anzahl der Kinder mit verschieden vielen durchgebrochenen 6-Jm.

Anzahl der vorhandenen 6-Jm	Vierjährige		Fünfjährige		Sechsjährige	
	Anzahl d. Kinder	%	Anzahl d. Kinder	%	Anzahl d. Kinder	%
0	553	98,9	439	77,8	137	27,2
1	2	0,4	33	5,9	45	8,9
2	3	0,5	58	10,3	111	22,0
3			11	1,9	27	5,4
4	1	0,2	23	4,1	184	36,5
Anzahl d. Kinder in den Jahresgruppen . . . .	559	100,0	564	100,0	504	100,0

In Tabelle 1 ist angegeben, wie viele Kinder der Gruppen Vierjährige, Fünfjährige und Sechsjährige (Durchschnittsalter

$4\frac{1}{2}$ ,  $5\frac{1}{2}$  und  $6\frac{1}{2}$  Jahre) verschieden viele 6-Jm haben. Wie man sieht, haben nur etwa 1 % Vierjährige bereits 6-Jm, unter den Fünfjährigen sind es etwa 22 %. Von den Sechsjährigen haben nur etwa 27 % noch keine 6-Jm, während 36 % dieser Jahresgruppe schon alle vier 6-Jm aufweisen.

Die 6-Jm, die in den einzelnen Kieferhälften die Ordnungszahl 6 des permanenten Gebisses tragen, stehen einige Jahre nach ihrem Durchbruch neben den Milchmolaren. Es dürfte für den Arzt, der bei der Untersuchung der Mundhöhle auch die Zähne in Augenschein nimmt, keine Schwierigkeit bieten, die 6-Jm von den Milchzähnen zu unterscheiden. Dagegen kommt es sehr häufig vor, dass die Eltern nicht wissen, dass ihr Kind bereits andere als Milchmahlzähne hat, obwohl schon 6-Jm durchgebrochen sind. Selbst wenn die Eltern bemerkt haben, dass das Kind drei Mahlzähne in den Kieferhälften hat, sind sie doch sehr oft überzeugt, dass alles Milchzähne seien. Wenn man bei einer Untersuchung der Kinder den Bescheid gibt, dass der hinterste Zahn kein Milchzahn sei, so kommt es z. B. nicht selten vor, dass die Angehörigen zunächst heftig protestieren. Diese Unachtsamkeit von seiten der Eltern hat oft zur Folge, dass viele 6-Jm auch in solchen Fällen zu spät zur Behandlung kommen, wo man sich bemühte, den bleibenden Zähnen jede nötige Pflege zukommen zu lassen.

Die 6-Jm werden in der Schulzahnpflege behandelt. In Schweden werden die Kinder mit dem Jahre schulpflichtig, wo sie 7 Jahre alt werden. Viele Kinder sind daher bei dem ersten Kontakt mit der Schulzahnpflege zwischen 7 und 8 Jahre alt. Die 6-Jm waren dann in vielen Fällen seit 1—2 Jahren dem Einfluss kariesfördernder Faktoren ausgesetzt. Sie sind auch zur Zeit der ersten Behandlung in nicht wenigen Fällen bereits so hochgradig kariös, dass eine konservative Behandlung nicht mehr in Frage kommen kann. In anderen Fällen bedarf es umfassender und auch für den Patienten beschwerlicher Behandlung, um die Zähne zu retten. An gewissen Orten, beispielsweise in Malmö, hat die Schulzahnpflege versucht, die Kinder ein Jahr vor Schulbeginn zur Untersuchung und Behandlung zu bekommen, um so die Möglichkeit zu erhalten, kariöse 6-Jm frühzeitiger zu behandeln. Die damit gemachten Erfahrungen sind sehr vielver-

sprechend. Wenn der Ausbau der Volkszahnpflege erst in vollem Umfang erreicht ist, wird eine solche Massnahme wie die eben genannte überflüssig sein, da dann alle schwedischen Kinder in der Volkszahnpflege die Möglichkeit zu regelmässiger Zahnuntersuchung und -behandlung nicht nur während der ganzen Schulzeit, sondern bereits vom dritten Lebensjahr an haben werden. Indessen muss man damit rechnen, dass noch viele Jahre vergehen werden, bis wir so weit sind. Gegenwärtig sind nämlich gewisse Teile Schwedens (hauptsächlich Landbezirke) noch ohne Schulzahnpflege. In diesen Fälle werden die 6-Jm in sehr grossen Umfang zerstört.

Von den einschlägigen schwedischen Untersuchungen gibt eigentlich nur die von ISACSSON (1917) die Anzahl der kariösen 6-Jm bei den Kindern des ersten Schuljahres an. Sie fand bei 283 Kindern durchschnittlich 3,5 durchgebrochene 6-Jm. In Durchschnitt waren pro Kind 2,9 Zähne kariös und 0,9 wurden als irreparabel beurteilt. Bezeichnende Zahlenangaben über den Kariesbefall der 6-Jm bei Kindern des ersten Schuljahres machen auch einige dänische Arbeiten. PEDERSEN, LONG und KISBYL (1940) teilen in einer Tabelle Zahlen aus einer Reihe von Untersuchungen an verschiedenen Orten Dänemarks mit, Kinder im Alter von 6—7 bzw. 7 Jahren betreffend. Zwischen 26 und 49,4 % der durchgebrochenen 6-Jm waren bei den einzelnen Untersuchungen kariös. In einer Arbeit vom Jahre 1944 teilen KROHN und PEDERSEN die Frequenz der kariösen 6-Jm bei Kopenhagener Kindern des ersten Schuljahres in den Jahren 1936—1943 mit. Im Jahre 1936 betrug die prozentuale Anzahl kariöser 6-Jm etwa 35. Die Zahl nahm dann laufend ab bis auf etwa 25 % im Jahre 1943. LIND und BRAMS (1941) teilen aus Nordjütland mit, dass etwa 80 % der durchgebrochenen 6-Jm bei den Siebenjährigen kariös waren.

Da eine so grosse Anzahl der 6-Jm schon im ersten Schuljahr kariös sind, muss man damit rechnen, dass diese Zähne bereits im vorschulpflichtigen Alter in grossem Umfang von Karies befallen werden. Dass dies tatsächlich der Fall ist, wissen wir aus Erfahrung. Wie oben erwähnt, kann das vom Verf. zusammengebrachte Material das Vorkommen von Karies der 6-Jm im Klein-

Kindesalter beleuchten. In Tabelle 2 ist für die Vier-, Fünf- und Sechsjährigen angegeben, wie viele der Kinder, bei denen 6-Jm durchgebrochen waren, Kariesbefall dieser Zähne aufwiesen. Betr. Untersuchungstechnik und Beurteilung des Befalls sei auf die Arbeit des Verf.s über Milchzahnkaries verwiesen.

Tabelle 2.

Anzahl der Kinder mit 6-Jm und mit kariösen 6-Jm.

	Vierjährige	Fünfjährige	Sechsjährige
Anzahl d. Kinder mit 6-Jm . .	6	125	367
Anzahl der Kinder mit kariösen 6-Jm . . . . .	1	36	176
% Kinder mit kariösen 6-Jm . .	(16,7)	28,8	48,0

Wie man sieht, ist Kariesbefall der 6-Jm häufig (48,0 %) bei Sechsjährigen, die überhaupt diese Zähne haben. Bei den Fünfjährigen ist der entsprechende Prozentsatz 28,8. Kariesbefall der 6-Jm finden wir auch bei einem Vierjährigen.

In Tabelle 3 ist angegeben, bei wie vielen der Kinder mit kariösen 6-Jm 1, 2, 3 oder 4 von diesen Zähnen kariös sind. Bei den Fünfjährigen sind, wie man sieht, meistens 1 oder 2 6-Jm schadhaft, während bei den Sechsjährigen 3 oder 4 kariöse 6-Jm keine Seltenheit sind.

Tabelle 3.

Anzahl der Kinder mit 1—4 kariösen 6-Jm.

Anzahl d. kariösen 6-Jm	Vierjährige	Fünfjährige	Sechsjährige
1		15	75
2	1	14	10
3		5	18
4		2	23
Anzahl der Kinder mit kariösen 6-Jm . . . .	1	36	176

Eine Übersicht über die Anzahl vorhandener und kariöser 6-Jm in den einzelnen Jahresgruppen bietet Tabelle 4. Bei den Fünfjährigen sind etwa 24 % und bei den Sechsjährigen etwa 31 % der durchgebrochenen 6-Jm kariös.

Tabelle 4.

Anzahl der vorhandenen und der kariösen 6-Jm.

	Vierjährige	Fünfjährige	Sechsjährige
Anzahl der vorhandenen 6-Jm .	12	274	1 084
Anzahl der kariösen 6-Jm . . .	2	66	341
% der kariösen 6-Jm . . . . .	(16,7)	24,1	31,5

Die überwiegende Mehrzahl der schadhaften Zähne zeigte nur Fissurkaries.

Symmetrisch auftretende Schmelzhypoplasien des bleibenden Gebisses führt man heute auf eine Stoffwechselstörung während der Zeit der Zahnschmelzbildung zurück. Es dürfte erwiesen sein, dass D-Vitaminmangel in den ersten beiden Lebensjahren häufig diese Störungen in der Zahnschmelzbildung der bleibenden Zähne im Gefolge hat. Dabei werden oft die 6-Jm von ausgedehnten Schmelzhypoplasien betroffen. Die Erfahrung lehrt auch, dass Schmelzhypoplasien der 6-Jm (ebenso wie anderer bleibenden Zähne) seltener werden, wenn die Kinder in den ersten Jahren eine Schutzdosis Vitamin D bekommen (PRINZ und SCHRAY, 1938). Die Ansichten über den Grad der Kariesresistenz von Zähnen mit Schmelzhypoplasie sind geteilt. Sicher scheint jedoch zu sein, dass, wenn solche Zähne erst einmal von Karies befallen sind, die Zerstörung sehr schnell fortschreitet.

In einer von SJÖHOLM (1944) veröffentlichten Untersuchung über das Vorkommen von Schmelzhypoplasien bei Malmöer Volksschülern heisst es, dass solche an den 6-Jm in 52 % im Oberkiefer und 60 % im Unterkiefer festzustellen waren.

Wir wollen nun in Anlehnung an die obige Übersicht mit einigen Worten die Möglichkeiten nennen, die der Arzt hat, für einen besseren Zustand der 6-Jm gegenüber dem heutigen zu

wirken. Die vorgetragenen Punkte betreffen in erster Linie schwedische Verhältnisse, lassen sich aber mit gewissen Modifikationen (beispielsweise bei früherem Schulanfang bzw. anderer Organisation der Schul- und Kleinkinderzahnpflege) auch von den Ärzten anderer Länder beobachten.

Beiläufig sei zunächst unterstrichen, dass eine systematische sog. Rachitisprophylaxe durch Darreichung von Vitamin D in den ersten Lebensjahren als zusätzlichen Gewinn bessere Möglichkeiten für eine gute Verkalkung der Zähne schafft. Der Arzt übt damit also eine Hypoplasieprophylaxe nicht nur für die 6-Jm, sondern auch für die übrigen Zähne des bleibenden Gebisses aus.

Die übrigen Möglichkeiten, auf die der Verf. hier hinweisen möchte, sind von sehr einfacher Art. Die erste besteht darin, dass der Arzt bei seiner Untersuchung der Kinder gelegentlich der Inspektion der Mundhöhle nachsieht, ob 6-Jm durchgebrochen sind, und dass er die Eltern darüber aufklärt, dass dies der Fall ist und dass es sich dabei um bleibende Zähne handelt. Besonders wichtig ist dies bei den Kindern der Jahrgänge vor Schulanfang (Fünf- und Sechsjährige) sowie älteren Kindern an Orten ohne Schulzahnpflege. Wird den betreffenden Eltern klargemacht, dass ihre Kinder schon bleibende Zähne haben, so ergibt sich daraus für viele Kinder die Möglichkeit einer frühzeitigen Kontrolle und, falls notwendig, Behandlung dieser Zähne. Die geringfügigen Beschwerden, die das für den Arzt mit sich bringt, werden mehr als wettgemacht durch die Dankbarkeit, welche die Eltern in vielen Fällen empfinden und ausdrücken. Es ist ein öffentliches Interesse, dass der Irrtum, die 6-Jm seien Milchzähne, bekämpft wird. Durch systematische Aufklärung darüber, dass die 6-Jm bleibende Zähne sind, erwirbt sich daher der Arzt kein geringes Verdienst um die bessere medizinische Einsicht des Publikums.

Eine andere Möglichkeit, einer Zerstörung der 6-Jm vorzubeugen, steht dem Arzt damit zur Verfügung, dass er, ohne eine genauere Untersuchung vornehmen zu brauchen, die 6-Jm inspiziert und den Eltern Mitteilung macht, wenn Kariesbefall bzw. der Verdacht eines solchen vorliegt. Da der kariöse Prozess sich häufig sehr schnell entfaltet, ist es dringend erwünscht, dass



Kinder mit solchen sicher oder mutmasslich schadhafte 6-Jm unverzüglich dem Zahnarzt zugeführt werden. Dies gilt besonders für die Kinder vor Schulbeginn (Fünf- und Sechsjährige) sowie für Schulkinder ohne Schulzahnpflege. In Fällen, wo das Kind zwar der Schulzahnpflege untersteht, man aber annehmen darf, dass die jährliche Untersuchung nicht innerhalb der nächsten zwei Monate stattfinden wird, dürfte es angezeigt sein, einen Besuch beim Zahnarzt anzuraten.

### **Zusammenfassung.**

Die 6-Jahrmolaren, die wichtigsten Zähne des bleibenden Gebisses, sind auch diejenigen Zähne dieses Gebisses, die am häufigsten durch Karies zerstört werden. Dazu trägt u. a. die Tatsache bei, dass diese Zähne von den Eltern sehr oft als Milchzähne angesehen werden. Es wird zahlenmässig beleuchtet, dass das Bedürfnis nach konservativer Behandlung der 6-Jm schon bei vielen Fünf- und Sechsjährigen vorliegt, also vor Schulanfang (in Schweden werden die Kinder in dem Jahre schulpflichtig, in welchem sie 7 Jahre alt werden).

Es wird auf gewisse Möglichkeiten hingewiesen, die der Arzt hat, um die frühe Zerstörung der 1. bleibenden Molaren zu verhüten. Die sog. Rachitisprophylaxe mittels Darreichung von Vitamin D in den ersten Lebensjahren bedeutet gleichzeitig eine Schmelzhypoplasieprophylaxe auch betreffs der 6-Jahrmolaren. Ferner soll der Arzt bei der Untersuchung von Kindern auch diesen wichtigen Zähnen einige Aufmerksamkeit schenken. Bei Fünf- und Sechsjährigen (sowie älteren Kindern an Orten ohne Schulzahnpflege) soll der Arzt die Eltern von dem Durchbruch der 6-Jahrmolaren unterrichten und sie darauf hinweisen, dass es sich um bleibende Zähne handelt. Wird sichere oder mutmassliche Karies der 6-Jahrmolaren festgestellt, so sind die schulpflichtigen Kinder sowie die Schulkinder an Orten ohne Schulzahnpflege dem Zahnarzt zuzuführen. Schulkinder mit kariösen 6-Jahrmolaren, die der Schulzahnpflege unterstehen, sind ebenfalls zum Zahnarzt zu schicken, falls die jährliche Untersuchung der Schulzahnpflege nicht kurz bevorsteht.

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## **Eosinophilia Leukaemoides.**

By

**PER SELANDER.**

Hyperleukocytosis with eosinophilia is a rare and puzzling syndrome. Scarcely more than 25 such cases with leukocyte counts above 25 000 are reported in the literature. There are, on the contrary, a great many cases with leukocyte counts lower than this, but the border-line between them and the common eosinophilic conditions in connection with asthma, parasites etc. is very vague. There are, further, published a great number of cases with eosinophilic leukocytosis which has developed during lymphogranulomatosis, metastasizing tumours and tuberculosis in the blood-forming organs etc., i. e. cases where a reasonable cause of leukocytosis and eosinophilia is already present. In the remaining cases, however, the origin has not been clear. In these latter cases it is especially their relation to leukemia that has been discussed.

LOTTRUP (1936) made a critical survey of the literature on such cases up to 1934. He arrived at the conclusion that no certain case of eosinophilic leukemia had ever been described. According to LOTTRUP the hypereosinophilic conditions that have been published, are more probably due to a number of different reasons. They seem to occur especially when several diseases coincide, which separately may elicit eosinophilia. Remarkably many of the published cases suffered from pulmonary or cardiac affections.

In 1942 the Danes ENGBAEK, HEERUP and THOMSEN took up this problem again and discussed it in detail. Contrary to LOTTRUP they recognize a genuine eosinophilic leukemia, to which they relegate cases with immature cells in the blood and proliferating

myeloid tissue in the organs. Only a small number of certain cases of this type are described (STEPHENS, 1935, THOMSEN and PLUM, 1939). In a further couple of cases the clinical course and the blood counts indicate that it probably must be the question of genuine leukemias (HAY and EVANS, 1928, FORKNER et al., 1937). In most cases the post-mortem examination revealed no leukemic changes at all, or only in one or two organs. For these cases the Danish authors propose the term »Eosinophilia leukaemoides», a term which seems to have been used for the first time by SCHMIDT-WEYLAND (1925). A 7-years-old boy with a leukocyte count as high as 165 000, of which 79 % were eosinophils, is described in the Danish paper. He showed changes in the organs which resembled histologically those found in allergic conditions or in anaphylactic shock. The authors therefore suggest that the symptoms in similar cases are caused by antigen-antibody reaction in persons with allergic constitution. In their opinion it should thus not be the question of a disease of the blood-forming organs. They suggest various antigens. — Some of the cases described in the literature suffered from asthma (ARMAND-DELILLE and DE PIERREDON, 1927, BASS, 1931, possibly also the case reported by BURKE and GUPTA, 1934), various intestinal parasites were found in a couple of cases (ARMAND-DELILLE and DE PIERREDON, 1927, BECKING, 1936), but in most of them no allergic diseases have been recorded, nor any definitely allergenic factors. The most common diseases in the anamnesis of these patients are diseases of the heart and the lungs, lues, malaria and disturbances of the internal secretion.

The clinical picture in eosinophilia leukaemoides is variegated, and, strictly spoken, the only common feature in these cases is hyperleukocytosis and hypereosinophilia in the blood and tissues. Enlargement of the *spleen* has however been a constant feature in nearly all cases as well as *fever*. The fever has often been of long duration; in 4 cases, described by VALLEDOR, MENDOZA and PEDRERA (1939), it lasted for several months. The highest leukocyte count found in one of the more carefully described cases was 230 000 (SHAPIRO, 1919). The eosinophilia has attained as high values as 75—80 %. In all cases the eosinophilic leukocytes

are described as mature, though sometimes of variable size with granules of different numbers and size, the nuclei distinct lobed and the protoplasm sometimes slightly basophilic. *Anemia* has not been a very conspicuous feature, nor have the *platelets* been changed. *Tendency to bleeding* is only reported once (BANG, 1942). A generally moderate *lymphadenopathy* was noted in most cases. *Enlargement of the liver* has been rather common. A notable roentgen finding, observed in all with this method examined children except one (BASS, 1941) are extensive miliary shadows in the *lungs*. They remained for a long time. None of these cases was examined post-mortally, and, consequently, the kind of these changes is unknown. *Cutaneous changes* are only reported by BASS (1931): an 8-year-old boy had a rash, which resembled erythema multiforme, on the abdomen. No objective *changes in the joints* have been observed. It is worth noticing that thrombotic changes in the heart were found in rather many cases at the post-mortem examination.

The *prognosis* is bad in cases with eosinophilia leukaemoides, though not so bad as is maintained by ENGBAER, HEERUP and THOMSEN (1942) who say that »all the cases of this kind described in the literature have had a fatal outcome». As a matter of fact only a couple of the 10 children with this syndrome, published up to now, seem to have died from the disease. One further case, a 2-year-old child, observed by POWERS in 1941, had a leukocyte count of 90 000, out of which 60 % were mature eosinophils; it died, but no post-mortem examination was performed, and we can therefore not say with safety if this was a case of eosinophilia leukaemoides. Even some adult patients seem to have survived (BÖEKELMANN, 1925, BURKE and GUPTA, 1934, PÉAN, 1938). Among the patients who have had leukocyte counts above 100 000 only one, however, a 21-year-old Hindoo, seems to have recovered (BURKE and GUPTA, 1934).

The clinical picture in the cases which lacked leukemic changes in blood and tissues did not show many features which indicated genuine leukemia. In these cases the characteristics of genuine leukemia, i. e. tendency to bleeding, progressive anemia, thrombocytopenia, ulcerative processes in the mouth, skeletal

changes etc., have been inconspicuous or even totally lacking. It is evidently the hyperleukocytosis, the unknown etiology and the bad prognosis which have led a number of authors to consider these cases to be leukemias.

In Europe only 4 cases of eosinophilia leukaemoides in children seem to have been described. DE BENEDETTI (1913) reported a 14-year-old boy with myxedema, arrested development, suspected congenital lues, urticaria etc., who had a white cell count as high as 78 000, of which 82 % were eosinophils. Course unknown. A 13-year-old boy, described by ARMAND-DELILLE and DE PIERREDON (1927), had a leukocyte count of 35 000, of which 85 % were eosinophils. This boy had suffered from malaria and had a severe asthma and 3 different kinds of intestinal parasites. For the rest the case report is too incomplete to allow of any definite conclusions as to its nature. BECKING (1936) writes on a 2 $\frac{1}{2}$ -year-old girl with a leukocyte count of 45 000 with the proportion of eosinophils as high as 62 %. The patient, who suffered from ascaris, trichocephalus and lichen urticatus, recovered. The 4th case, published by ENGBAER, HEERUP and THOMSEN (1942), has been mentioned above.

For nearly 2 $\frac{1}{2}$  year the present author has had the opportunity of following a case belonging to this group of diseases, and which may be interesting especially as the patient recovered in spite of high leukocyte counts.

Girl, born 10.6, 1939. Admitted to the hospital on Dec. 14, 1942. — Healthy parents. The patient was No. 5 of a family of 9 children, of which one had died from scarlatina. The remaining children were healthy. (As for their blood counts and state of health see table 4.) No serious diseases in the family. The patient has had measles and symptoms of adenoid growths, but for the rest always been healthy.

About Dec. 1, 1942 the patient fell ill with a cough and fever. 4 days later a rash appeared on the fingers, at first consisting of small red purulent pustules. They itched intensely. At the same time pruritus set in all over her body. After some days the rash was found here and there on her body, though mostly on the hands and feet, which ached so much that she cried aloud. Gradually the hands, the feet, partly also the trunk and the face, became swollen. The temperature during the last 9 days before admittance varied between 38°.3—40°.5 C.

Poor general condition when admitted. She was very swollen all



Fig. 1. Cutaneous changes after 14 days' disease.



Fig. 2. Cutaneous changes after 1 month's disease. Mark the sharp limit towards the face and the necrosis on the left ankle.

over the body, especially on the hands. For the rest the most dominating feature was the *cutaneous changes*. On nearly the whole trunk a partly red, partly yellow-brown rash was observed, forming slightly elevated nearly palm-sized spots, which were beautifully serpiginous almost everywhere (Fig. 1). On fingers and toes a great number of small pustules, filled with pus. Larger blisters, filled with a thin purulent content, were found on the palms. — *Temperature*: 39° C. — *Heart, lungs, throat, lymph nodes, blood pressure, capillary resistance*: normal. Reaction to MANTOUX test with 1 mg negative.

*Laboratory Data*. — *Urine*: normal. *Fecal examination*: no ova. WASSERMANN reaction: negative. BUNNEL reaction: negative. *Roentgenograms* of heart, lungs, mediastinum and skeleton: normal. *Electrocardiogram*: Dec. 29, Jan. 11 and March 16: normal. *Seroreaction for trichinosis*: negative. *Culture from blister in the hand*: no growth.

*Biopsy on cutaneous infiltration*. — »In several places in cutis, but not in subcutis, perivascular phenomena with large numbers of eosino-

Table 1.

Results of Blood Counts in the Patient.

Date	Hemoglobin Content, per Cent (Haldane's Standard)	Red Cells, Millions per Cu. Mm.	White Cells, 1 000 per Cu. Mm.	Platelets, 1 000 per Cu. Mm.	Neutrophils, per Cent	Eosinophils, per Cent	Lymphocytes, per Cent	Monocytes, per Cent	Sedimentation Rate (Ström's Mikromethod)	Remarks
12/16/42	85	5.60	78.0	249	20	53	25	2	4	{Promyelocytes and myelocytes 2 per Cent
12/18/42	—	—	62.6	—	8	48	40	2	—	
12/21/42	79	—	94.9	—	20	37	40	3	18	
12/24/42	—	—	102.6	—	24	34	38	4	—	
12/27/42	74	—	63.6	—	19	38	40	3	—	
12/30/42	74	—	50.0	564	14	61	21	4	45	
1/6/43	94	4.20	37.0	440	6	58	31	5	—	
1/20/43	88	3.88	21.5	318	16	36	43	6	21	{Basophils 0.25 per Cent
2/11/43	83	4.82	23.5	338	23	43	29	5	39	{Scarlet fever.
2/17/43	83	3.76	25.7	273	22	57	20	1	36	{Otitis. Nephritis
4/14/43	81	3.70	15.6	439	14	30	55	1	28	{Basophils 0.75 per Cent
6/2/43	80	4.38	12.7	282	20	36	39	5	23	
6/21/43	89	3.97	16.2	230	76	1	20	2*	47	{Pneumonia
6/28/43	80	4.16	20.1	334	68	10	14	7*	58	{Polyarthrits
7/6/43	66	2.87	8.4	330	28	27	41	4*	63	{350 Cc. of Blood intra-venously
7/15/43	77	3.62	8.4	266	48	7	41	6	40	
10/30/43	84	—	7.6	284	23	4	69	4*	8	
2/12/44	89	4.5	8.6	336	21	6	73	0*	6	
3/8/45	—	—	—	—	53	10	29	8	—	

phils. In some places the endothelium a little swollen. No thrombi, no necroses, no signs of periarteritis nodosa or any other kind of vascular allergy. Epidermis, larger vessels and nerves normal. The above-mentioned vascular infiltrations do not resemble leukemic infiltrations. — The process in the examined piece of skin can be classified, generally spoken, as an eosinophilic dermatitis» (GELLERSTEDT).

*Blood:* Prothrombin content and bleeding time: normal. See table 1. (For want of space only some of the blood counts are published. — The



Table 2.

Results of Differential Counts of the Nuclear Segments of the Eosinophilic Cells.

Date	Number of Segments of the Nuclei				
	1	2	3	4	5
12/18/42	11	35	38	14	2
12/30/42	1	37	39	13	10

counts marked \* in table 1 were calculated on 100 leukocytes only, while all the other published data refer to at least 400 counted cells.)

At one examination in the beginning of the disease a few per cent eosinophilic promyelocytes and myelocytes were found in the blood, but, during the whole time of observation, the majority of the eosinophils were adult cells with a segmented nucleus (Fig. 3). The differential count of the lobes showed that the normal 2-lobed nucleus only occurred in about 35 %, while most of the eosinophils had a still more lobed nucleus (Table 2). For the rest the nuclei did not seem definitely abnormal. The cells were of normal size, with rather large granules, distributed irregularly in the protoplasm. Colour of protoplasm: normal.

*Sternal Marrow.* — At the first examination almost only eosinophilic cells were found in the sternal marrow. They varied very much as to size, the granules were distributed irregularly, and the protoplasm was strongly vacuolar. Indistinct nuclei, which stained badly and were strongly vacuolar. The cells are best characterized as promyelocytes (See table 3 and fig. 4).

*Course.* — During the first days the patient's condition was extremely poor, but after about 1 week she began to recover. The temperature kept between 38°—39° C. for the first 2 weeks and then fell and remained subfebrile. The spots in the skin spread over the whole trunk, and changed into blue-red and, later, brown extensive infiltrations. They formed a distinct border towards the face (Fig. 2). The blisters on the hands and feet gradually dried. The fingers remained woodenly swollen for a long time, and there was further a protracted doughy swelling of the fore-arms. No hemorrhages in the skin. — The lymph nodes in the axillas became palpable — some became as large as beans — while no certain enlargement of other nodes could be observed. The spleen was not palpable. — By and by the skin became dry and scaly and very cracked, and ulcerations developed at the joints. — The appetite returned, and the recovery proceeded fairly rapidly.

On Jan. 23, 1943, the patient contracted scarlatina at the same

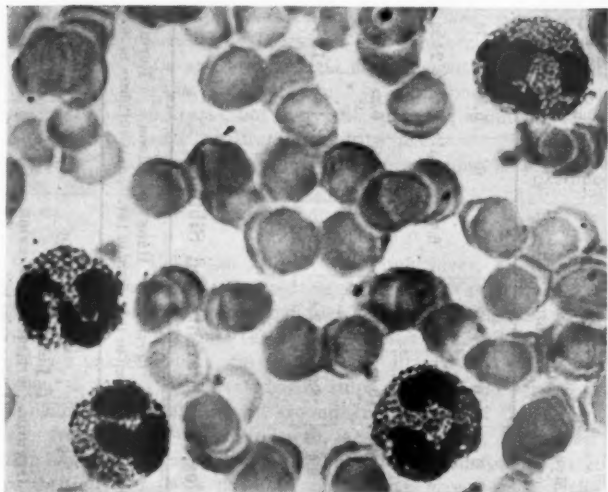


Fig. 3. Blood. Eosinophilic cells with markedly segmented nucleus.

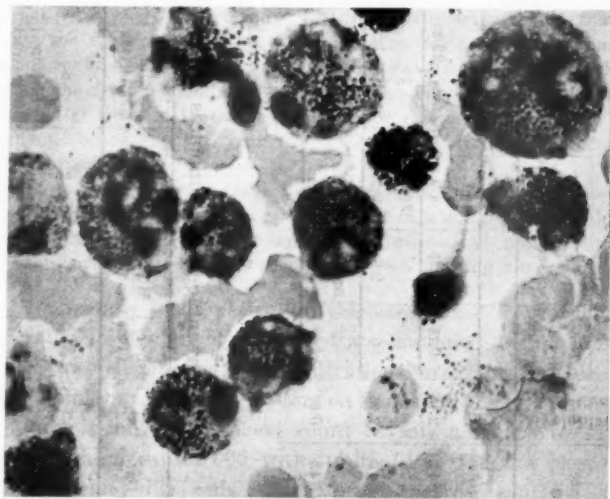


Fig. 4. Sternal marrow. Almost only eosinophilic cells.

Table 3.  
Results of Differential Counts of the Cells in the Sternal Marrow.

Date	Myeloblasts, per Cent	Eosinophils, per Cent					Neutrophils, per Cent					Lymphocytes, per Cent	Leukocytes, per Cent	Nucleated Erythrocytes, per Cent
		Pro- myelo- cytes	Myelo- cytes	Meta- myelo- cytes	Stab forms	Seg- mented forms	Pro- myelo- cytes	Myelo- cytes	Meta- myelo- cytes	Stab forms	Seg- mented forms			
11/14/42	0			93			0	0	0	0	0	0	6.35	1.75
1/4/43	2.75	0.75	4.25	4.0	3.25	22.25	6.75	6.25	3.75	4.75	6.0	9.75	1.25	24.25
3/14/43	2.25	0	2.0	2.25	1.25	1.25	17.75	7.25	10.25	9.75	14.5	26.25	0.25	5.25
9/4/43	0.6	1.0	2.0	1.8	1.4	2.1	12.20	6.8	8.2	12.4	13.0	21.0	4.6	12.4
				8.3										

Table 4.  
Percentage of Eosinophils in Blood Samples from Parents and Siblings.

Date	Father born in 1905	Mother born in 1908	Maj born in 1930	Ella born in 1935	Gunvor born in 1936	Clary born in 1938	Bertil born in 1941	Hans born in 1942	Mona born in 1943	Karin born in 1945
9/4/43	4 Healthy	3 Healthy	2 Healthy	6 (Lichen urticatus)	2 Oxyuris	9 Oxyuris	9 {Lichen urticatus, Oxyuris}	16 Eczema	—	—
9/6/45	4 Oxyuris	6 Healthy	1 Healthy	7 Healthy	2 Oxyuris	6 Oxyuris	1944 {Scarlet fever, Oxyuris}	12 Eczema	8 Ascariis	3 Healthy

time as another patient in the same ward, and was therefore referred to the Dept. for Infectious Diseases. Her scarlatina was complicated by suppurative otitis and hemorrhagic nephritis with large edema. The patient returned to the Children's Clinic in good condition on March 16. The ulcerations had healed, but there still remained a number of sharply limited, red cutaneous infiltrations on the trunk. — *Lymph nodes* in the axillas, the neck and the groins: from pea- to bean-sized. — *Spleen* still not palpable. — *Inner organs* otherwise normal. — *Normal temperature*. — The patient was discharged on May 4, 1943, in very good condition.

On June 14, 1943, she fell ill with high fever, difficult respiration and convulsions. Readmitted on June 21. Was found to have a rightsided pneumonia. Some small red cutaneous infiltrations were observed on the trunk, and, further, small necroses and blisters at the wrists and ankles. She again became very ill and lay with high fever for about 4 weeks. Was treated with sulphathiazole and sulphapyridine. The pneumonia was cleared up around July 12. — At that time nearly all the *finger joints* began to swell, and the *wrists, knee joints and ankles*, too. The joints became stiff and tender, almost as in chronic polyarthritis. — *Lymph nodes* in the axillas, groins and in the neck were markedly enlarged this time. — The *spleen* was palpable about 2 fingerbreadths below the costal margin. — The *liver* was not palpable. — When, this time, the *hemoglobin content* showed a tendency to drop, the patient was given a blood transfusion. The temperature fell gradually, the appetite returned, especially after an arsenic cure, and the patient could be discharged on Sept. 28, 1943, in very good condition. During the first 6 months after leaving the hospital small ulcerations appeared at times at the ankles, but for the rest her condition has been excellent. Since about 1 year she is free from symptoms except for some eosinophilia.

The patient's parents and siblings have been examined on two occasions (Table 4). Eosinophilia was observed in a couple of the siblings, but was explained by the presence of parasites, lichen urticatus and eczema. For the rest their blood pictures show nothing abnormal.

*Discussion.* — The patient in this case is a 3 1/2-year-old girl who falls ill in a highly febrile state, attended with cutaneous changes, as edema, massive infiltrations over the greater part of the trunk, pustules and blisters on hands and feet. Pronounced pain and itching. The blood count reveals a leukocytosis with values as high as 102 000 with up to 61 % for the most part mature eosinophilic cells. The sternal marrow contains about 90 % eosinophilic cells. Biopsy of the skin shows an unspecific

picture with eosinophilic cells. Later on swelling of the joints, general lymphadenopathy, and, during one period, distinct enlargement of the spleen developed. — In spite of the patient's happening to contract scarlatina, suppurative otitis, hemorrhagic nephritis and pneumonia, the disease is cleared up. The leukocytosis returns to normal values after some 6 months. A slight eosinophilia remains, however, still 2 years later.

In the literature no case of eosinophilic hyperleukocytosis with skin and joint changes, resembling those found in the present case, has been described. When comparing the various published cases it is conspicuously difficult to fit all of them into one acceptably homogeneous clinical entity. It is only some cases from the West Indies which make a more uniform impression (BASS, 1931, VALLEDOR, MENDOZA and PEDRERA, 1939, VALLEDOR, FERNÁNDEZ-BALTRONS and EXPÓSITO, 1942); some of these works have, however, not been accessible here in the original publication. — The present case as well as most of the reported ones is characterized by a complex of symptoms from different organs.

The blood, the sternal marrow and the excised piece of skin from the patient proved to be inundated by eosinophilic leukocytes. If it had been possible to examine other organs histologically, it seems probable that the same phenomenon would have been met with there, too. If the patient had died — and her condition was at times so bad that it seemed almost miraculous that she survived — this case would have been interpreted as an eosinophilic leukemia for the same reasons as in most of the earlier published cases. The outcome proves, however, that it was never a question of this disease.

Probably most of these cases are no leukemias. This is *inter alia* indicated by the fact that the syndrome in most cases developed in subjects who already suffered from one or the other disease. ENGBAEK, HEERUP and THOMSEN's suggestion of some kind of allergy as the cause of this clinical picture might explain much of what has seemed obscure in these cases. In the present case, too, the skin and joint changes may very well be supposed to be of allergic origin; it is, as a matter of fact, difficult to imagine any other cause. If this theory be correct there is a risk of the

patient's falling ill again with similar symptoms. What the supposed hypersensitivity depends on is a seemingly unsoluble problem — there is probably a different cause in each case. It is, further, absolutely inexplicable why the eosinophilia and the leukocytosis sometimes attain such enormous proportions. It should be noticed that, in the present case, the blood picture did not deteriorate markedly either after the scarlatina, the otitis or the pneumonia. On the contrary, the eosinophilia disappeared during the last-mentioned disease.

The post-mortem examination in the published cases of eosinophilia leukaemoides often showed various kinds of changes in the heart and the lungs. It seems probable that some of these changes ought to be regarded as complications. The children's better circulatory organs should guarantee fewer and less dangerous complications, and this is perhaps the reason why the prognosis in eosinophilia leukaemoides in children is fairly good. The knowledge of cases with this clinical picture in children, and its relatively good prognosis, is of a certain interest as it indicates that a similar clinical picture must not necessarily be interpreted as a genuine leukemia in adult persons. From the occurrence of this disease in children we are justified in concluding that, however hopeless it may seem, everything should be done to save the patient as the changes evidently may be reversible.

As nothing definite is known about the origin of this disease it seems as yet best to call it eosinophilia leukaemoides, in accordance with SCHMIDT-WEYLAND (1925) and the Danes quoted above. We have to remember, however, that it is probably not the question of a uniform clinical entity.

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## **The Relation between Infantile Tetany and Rickets.**

By

**STURE SIWE.**

The question of a connection between infantile tetany and rickets is of very old standing. Even before the various symptoms of the former syndrome had been moulded into a sharply-defined clinical entity, KASSOWITZ pronounced his opinion that the manifest symptoms, the spasms, were due to hyperemia in the rachitic cranial bones with an ensuing irritation of the cerebral membranes and cortex. All rachitic cases did not show such symptoms of irritability, however. There must, therefore, be some factor predisposing to spasms in the rachitic cases which contracted tetany. KASSOWITZ suggested the presence of a neuropathic constitution.

The various symptoms of hyperirritability in spasmophilia were gradually collected by i. e. THIEMICH, MANN, FINKELSTEIN, into one homogeneous pathological picture with hyperirritability as a latent sign and tonic or clonic spasms as manifest symptoms. As these signs of hyperirritability, contrary to the symptoms of rachitis, as a rule subsided when cow's milk, and especially whey from cow's milk, was removed from the diet, and manifest clinical symptoms of rachitis could not always be observed — at this time roentgen examinations and blood analyses had not come into use — the infantile tetany was considered to be relatively independent of rickets.

During his whole life KASSOWITZ protested against such an opinion and was supported by other investigators. Both CZERNY and PFAUNDLER wanted to make an exception at least for the



common spasms. The former even spoke of a »cerebral rickets» which appeared as attacks of chronic spasms. KLOTZ went further still and included also the simple hyperirritability phenomena and the spasms, i. e. as complications of the primary disease — rickets. HESS, FREUDENBERG and GYÖRGY are of the same opinion: rickets predisposes to spasmophilia. Without rickets no spasmophilia. A certain type of constitution might, however, play a part in the development of the symptoms. And with this we are back again at KASSOWITZ's original point of view.

But this conception of the development is too superficial. During the discussions the question of the relationship between the two clinical pictures has deepened. According as the diagnostic methods have become more refined, the clinical symptoms have been connected up with other phenomena. Nowadays we do not discuss spasmophilia and rickets, but spasmophilic or rachitic disturbances in metabolism respectively, which may be diagnosed by more or less exact methods long before the clinical investigation detects the old accepted signs of the diseases in question. We speak of retarded or accelerated metabolism, of acidosis or alkalosis, of ionization, distribution of ions and action of ions. If we are more careful, more interested in clinical practise, and less active theoretically, we await with HESS the results of further investigations before defining more closely our opinion of the nature of this relationship. One fact only seems to be accepted by nearly everyone: there is a connection between the two diseases. The question is how this connection should be defined.

From a purely logical point of view this relationship may be of three different kinds: Rachitic disturbance in metabolism is a prerequisite of spasmophilia. As mentioned earlier, this is the most common and also the oldest opinion, at present supported especially by HESS and the Heidelberg school. Second, spasmophilia predisposes to rickets. As far as I know this possibility is not taken up by anyone; SHIPLEY—PARK—MCCOLLUM consider their low calcium metabolic disturbance with spasmophilia as a constant symptom as a form of rickets, too. Finally, the two diseases are parallel, developing from one and the same disturbance, which sometimes produces the one, sometimes the

other disorder, and often both at the same time. My own investigations have led me to the last viewpoint.

Let us for a moment look at the relationship from a purely clinical point of view. The age of predilection is the same in rickets and in spasmophilia. As shown in an earlier study (SIRWE 1934) *spasmophilia is not at all uncommon during the first few months of life*. In my material no less than 24 cases are < 6 months old. It does not follow, however, that spasmophilia is more common than rickets at this age, as the cramps, being more alarming symptoms, very naturally cause the children to be taken sooner to hospital. It should on the other hand be stressed especially that tetany is not too infrequent in adults, where rickets is never found.

The two disorders show the same seasonal variations with a peak in April, and the same distribution over different age groups during the two first years of life. If they become manifest, they are both cured by ultra-violet irradiation and vitamin D. As far as I can see, these clinical facts indicate a definite correlation between them.

Some investigators are, however, not satisfied with this. They suggest instead an interdependence of the two diseases, the one is considered the prerequisite of the other. Rickets is given the rôle of *causa prima* — rickets is a prerequisite of spasmophilia — »this sequence constitutes the significant feature in the clinical relationship between these disorders» (HESS). GYÖRGY chooses a more careful wording when saying that the two diseases reflect each other, that they represent the same disease at different stages. When confronted with such thoughts it is necessary to go back to the primary material in the clinic and in the laboratory and examine how far it supports such interpretations.

As regards the clinical manifestations, firstly, it is not sufficient that the frequency curves as a rule correspond — which we are able to confirm, too. If rickets is a necessary condition for spasmophilia, rickets must be found and proved, not only supposed, in *all* cases of spasmophilia if the sensitive methods for determining Ca and P are used regularly. In HESS's experience

the two diseases always coincide. But he mentions on the other hand that in his material (from the northern parts of the U. S. A.) rickets occurs in nearly 100 % among thousands of arbitrarily chosen children in the ages concerned. Under such circumstances there would scarcely be any disease in those ages and at those seasons that did not show a constant coincidence with rickets, and there is no possibility of proving that it is connected with rickets as a predisposing factor. We would be just as much justified in asserting that spring infections were due to rickets. To decide this point it is obviously necessary to study a material where not everyone suffers from rickets.

Is rickets as a matter of fact always found in spasmophilic infants? The fact that rickets does not occur in older children or in adults with tetany need perhaps not be discussed. But how is it during the first years of life? As I have shown in an earlier detailed study of cases from this clinic (SIWE 1934) many cases of spasmophilia show no signs whatever of sustained or florid rickets (when examined roentgenologically and with regard to the blood chemism) — this has also been confirmed by later experiences. This holds good in about 8 % of our material of about 200 cases with spasmophilia. A demonstrable rachitic condition can therefore not be supposed to be the foundation of spasmophilia.

If rickets were the foundation of spasmophilia, the latter clinical picture might be expected to occur later, i. e. its highest frequency should be found in somewhat higher ages than the former, and also later in the rachitic season. According to HESS this is also the case. »Tetany develops somewhat later than rickets.» He gives no figures.

Our clinical material (about 200 cases) does not support this view. The cases of spasmophilia are distributed over different ages just as rickets with a maximum in the 3rd and 4th quarters of the first year of life, and over the different months in the same way as rickets with a peak in March—April. Their frequency does not increase at the end of the rachitic season, on the contrary the opposite is more often the case:

## Spasmophilia is found

in 86 % of all rachitic cases in December,									
» 73 %	»	»	»	»	»	»	»	»	January,
» 71 %	»	»	»	»	»	»	»	»	February,
» 77 %	»	»	»	»	»	»	»	»	March,
» 57 %	»	»	»	»	»	»	»	»	April,
» 54 %	»	»	»	»	»	»	»	»	May, and
» 20 %	»	»	»	»	»	»	»	»	June.

Assuming that spasmophilia does not develop until rickets has gone on for some time, it is not easy to understand that the highest percentage is found in December, and a considerable lower percentage in April—June, if we do not want to believe that our rachitic cases are brought to hospital in earlier and earlier stages as the season goes on. Such an assumption lacks every support, however.

Spasmophilia is further found at lower ages than the chemically and roentgenologically demonstrable rickets. While the distribution of the cases of spasmophilia over the first 6 quarters of life is the following: 3 % — 14 % — 30 % — 21 % — 16 % — 12 % (and at ages above 1 1/2 year — 4 %), the corresponding distribution of the cases of rickets are 0—3 % — 22 % — 22 % — 16 % — 11 % — 26 %.

I conclude: In the material from our clinic spasmophilia shows the same distribution over ages and seasons as rickets. It does not occur at later ages or later in the season — rather the opposite.

Before leaving the clinic I want to point out that, according to old experience, some years are »tetany years» and others »rickets years» and that an increased frequency of rickets, as for instance in Germany after the first World war, need not imply an increased frequency of spasmophilia. Of course this does not prove that no connection exists — one might always explain these circumstances by assuming a variation in some eliciting factor without releasing the theory of rickets as a necessary foundation. But in so doing a new and unknown factor has been introduced, disturbing the plain relation of cause and effect which was assumed between rickets and spasmophilia.

In the case of such a disease as rickets we must, however, be exceedingly careful when drawing conclusions on the basis of clinical material. I have earlier and on several occasions discussed and proved that the clinical symptoms are very difficult to assess, especially in the first stages. The metabolic disturbance which is the foundation of rickets, may, or rather, must have lasted for some time before we are able to settle the diagnosis. This refers not least to the roentgenological examination, which is of limited value when judging, at a given occasion, if the process is active or not, if it is progressing or subsiding. The most sensitive indicators of a rachitic disturbance in metabolism are the changes in the blood and their effects. It is therefore natural that these changes have been submitted to detailed examinations to obtain support for the assumed connection between rickets and spasmophilia. Most investigators have reasoned in about the following way: The fundamental basis of rickets is a metabolic disturbance which causes an increased excretion of acid products in the blood. This must alter mutual relations of the blood phosphates and lead to an increased excretion of acid phosphates in the urine. By determining this excretion the relation between primary and secondary phosphate in the blood may be calculated. It is then found that rickets is accompanied by acidosis. Under certain circumstances — climatological factors and, to some extent, constitutional factors have been suggested — this retarded metabolism may change to the opposite: an accelerated metabolism. There is a relative phosphate stasis in the blood and alkalosis ensues. But this alkalosis leads to diminished ionization of calcium in the blood. Considering the diminishing action of the Ca-ion on the irritability in nerve and muscle preparations it seems possible that alkalosis might create a condition of hyperirritability, a condition which might even result in cramps of general nature. — Similar conditions with cramps or hyperirritability can be elicited in other ways, too: by hyperventilation or by supplying large doses of bicarbonate. But these measures cause alkalosis, too. The phosphorus content of the blood may be increased by giving alkaline phosphates — the relative phosphate stasis had the same effect — and the ionization of calcium consequently

diminished. This measure, too, elicits hyperirritability in experimental animals and induces the manifestation of a latent spasmophilia in children. Finally: The  $P_h$  of the blood may be diminished by the administration of acid salts per os and, consequently, the Ca-ionization enhanced, which results in the disappearance of the symptoms of hyperirritability and of the cramps. For these reasons salmiac was introduced among our symptomatically acting drugs in the therapeutical treatment of spasmophilia.

The discussion above, and the analogies, seem most attractive, and the hypothesis exceedingly plausible. But is it tenable?

For the first: Is there a retarded metabolism with increased acid intermediary products in the blood in rickets? The basis of this contention, as given by the Heidelberg school, the determinations of the phosphate in the urine, has been shown by e.g. Brock to be incorrect. Nevertheless the contention holds good. In several cases I have been able to prove convincingly by determining the organic acids in the urine that there is a considerable increase (toward 30—40 times the normal amount) of the acid intermediary metabolic products in the urine in rickets. This increase subsides very slowly according as the disease heals. But — and this is the most important aspect — no corresponding decrease occurs in spasmophilia. If this disorder is complicated by rickets, the increase is just as marked as in the cases of pure rickets. In spasmophilia the excretion never falls below the normal limit, and the metabolism does not tend to alkalinity — this is probably the decisive point. Some American investigators and DRUCKER here in Scandinavia have arrived at the same conclusion, although on other ways. The fact remains that the pendulum does not swing over.

Are the  $P_h^-$  values in the blood diminished in rickets and increased in spasmophilia? The informations vary on this point. This variation seems to me to be due at least partly to the relative inaccuracy of the methods, which makes even contradicting data seem equally credible.

Is there a relative phosphate stasis in the blood when rickets has healed? Yes, it seems to be confirmed from all quarters that

the blood phosphorus increases in that stage. But does the calcium in the blood diminish simultaneously, so that the rather typical chemical picture of spasmophilia develops? The answer is no. On the contrary it is the rule that when rickets heals not only the blood phosphorus but also the calcium in the blood increases. If I compare 35 cases of pure rickets with no signs of healing with 22 cases of pure rickets with marked tendencies to healing, the phosphate values in the former group are found to be 4.6, and in the latter 5.87 mg%, while the calcium values in the former group are 9.2 and in the latter 9.77 mg%, in spite of the considerably higher phosphate values in this group. When the phosphate values increase during the healing stage of rickets the calcium values still do not fall even if spasmophilia is present — perhaps with the exception of the first few days. In two groups with about 30 cases of spasmophilia in each I found the phosphate value to be 5.6 in the group where there were no signs of regression of rickets, and 6.75 mg% in the group with signs of regression. The calcium values in the former group were 6.7 and in the latter 6.6 mg%, thus not markedly lower than in the first group in spite of the considerably higher phosphate value. — A number of investigations have shown to what extent calcium may be increased in spasmophilia by means of symptomatic drugs as hydrochlorid acid or salmiac, and by the administration of parathyroid hormone or of vitamin D — the phosphorus always increases at the same time. Even if I give  $\text{CaCl}_2$  intravenously not only the calcium in the blood but also the phosphorus increase. All types of spasmophilic therapy tested out in the clinic increase not only the calcium but also phosphorus in the blood.

Some authors have advanced the opinion that it does not refer to the total amount of calcium but only to the ionized fraction. There is, however, no acceptable method of measuring these fractions. In ultra-filtrations of the blood some part of the calcium is precipitated. About  $\frac{2}{3}$  of this calcium fraction is by all authors in this field considered to consist of ionized calcium. If the calcium content in ultra-filtrates is examined, no decrease is found in spasmophilia nor any increase when it has healed.



Neither does the quickly and surely acting acidotic therapy increase the ultra-filtrable fraction of serum CaP.

In my opinion this brilliant hypothesis needs to be supported by exact examinations. I think that especially the abrupt change in metabolism is very loosely founded.

The cause of this sudden change seems also rather far-fetched. A hormonal crisis in the spring has been mentioned as a causative factor. The only observable phenomenon is the increased intensity in growth in spring and its consequences. But according to all clinical experience such an increase ought rather to exert a directly aggravating influence on rickets. Some meteorological factors, which are supposed to elicit this sudden change, also seem to be very vaguely defined. The only objective observation is, far as I can see, the fact that tetany sometimes appears in rachitic children when the sunshine increases in spring — as also in actinotherapy of rachitic children in the clinic. But the reason for this need not be sought farther than in the increase of phosphate in the blood and in the increased demand on blood calcium in the healing stage of rickets, as has been pointed out by GREENWALD. The same risk may be incurred by increasing rapidly the phosphate content of the blood by direct administration. — As shown above, the relative frequency of spasmophilia was even higher in December—March than during these spring days.

Thus, the metabolic studies and the examinations of the blood chemism do not yield any proofs of the theory that rickets predisposes to spasmophilia. It is quite another thing that an incipient rickets with its often slightly decreased calcium level in the blood as well as a rapid healing of rickets — spontaneous or artificial — with its accompanying increased demand on calcium to repair the changes in the bone tissue may play a certain rôle for the manifestation of spasmophilia. The majority of the cases of spasmophilia do not offer any possibilities of assuming a direct connection between the two diseases.

Up to now I have regarded the problem from purely negative points of view. Negations only are not much to build on and I should like to finish this survey with something positive, even



if it is nothing but my own attempt at understanding, thus — a hypothesis.

Neither clinical nor laboratory investigations have succeeded in showing that spasmophilia develops on the basis of rickets. The reverse has never been seriously suggested. The mutual relations of the two diseases must therefore be considered coordinate. As our daily clinical experience shows, they coincide in the great majority of cases at the same ages, and during the same seasons. They are prevented by the same measures and cured in the same way.

Lack of sunshine or vitamin D is the primary etiological factor in both diseases. This lack influences the whole organism. In most cases metabolism is most disturbed. This takes place independent of sex. Rickets sets in with an increase of the acid products in the blood and in the urine, and with lowered calcium and phosphorus contents in the blood. Later on the calcium content is mostly found to be normal while the phosphorus has fallen lower still. — Do the acid metabolic products accumulate by and by in the blood and begin to exert an influence there? This problem ought to be studied by further investigations on cases of pure rickets. And is the sudden change in the blood calcium connected with a lack of compensatory hyperactivity of the parathyroid glands, which become enlarged in rickets? The increased decalcification of the skeleton might point at such an explanation.

In some cases it is not the metabolism, however, which evinces the greatest susceptibility to the avitaminosis but instead the parathyroid glands. Their capacity of regulating the calcium content in the blood by means of withdrawing it from the bones decreases, and we may observe a lowered or at any rate badly regulated calcium level in the blood, and spasmophilia. The sensitivity is individual, perhaps linked to family, perhaps to locality. The constitution, of which the old clinicians spoke, comes to the fore again.

The rôle played by the parathyroids is one of the most-discussed aspects of this problem, for that very simple reason that only the parathyreoprivic tetany resembles in detail the

spontaneous infantile tetany. Some have however denied it any importance whatever. Their reasons are summarized by PINCUS—PETERSON and KRAMER, and given below.

1. The parathormone does not exert a constant curative effect in cases of spasmophilia. — HESS, GRÖRGY, and several others are of the opposite opinion. We have to remember that hormone preparations are often rather incalculable as to effect — probably the parathormone was more uncertain earlier than at present.

2. Ultra-violet irradiation cures the spontaneous spasmophilia but has no effect on the parathyreoprivic variant. — This objection seems rather remarkable, as it presupposes a substitutionary relation between the hormone and vitamin D, which none has suggested. The two factors may act together on the regulation of calcium. In one case the action of vitamin D is lacking. As regards the calcium content this may be substituted for a time — but only for a time — by the increased action of the parathyroids, or possibly by the administration of extracts. In the second case there is not sufficient glandular substance for the vitamin D to act on. In such cases vitamin D in ordinary doses cannot of course replace the removed glands. The sites of action of vitamin D and of parathormone are further not the same. The effect which cannot be attained by means of pure vitamin D, is obtained by the cognate substance A. T. 10. Its effect suggests in certain respects that of the parathormone: both increase the lability of the phosphorus concentration in the blood. In other respects it is more like vitamin D: the calcium-phosphate level in the blood is normalized for a shorter or longer time.

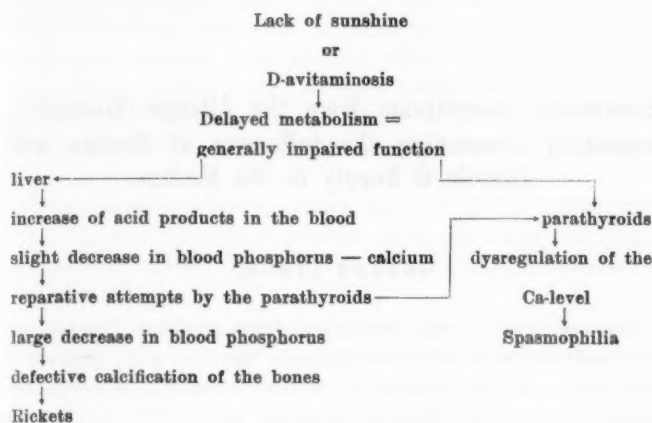
3. Finally: According to the above-mentioned authors there is a constant, very marked increase in phosphorus in the blood in parathyreoprivic tetany, which is missing in the spontaneous tetany. — My experiments have not confirmed this objection. Even late during the convulsive stage the animals with removed parathyroids show only an inconsiderable increase in phosphorus, together with strongly lowered calcium content. Only at the very end — death is always the outcome — the amount of phosphorus is enormously increased, while the calcium does not fall to the minimal level.

4. Anatomical changes are lacking. — But according to my opinion they could not very well be expected in such an easily reversible functional disturbance.

If we consider spasmophilia as a relative insufficiency of the parathyroids, it is not difficult to understand that the individual constitution must be a factor in its development. It is also clear that this insufficiency will appear as spasmophilia if rickets is present at the same time. Rickets increases, as we know, the demands on the calcium-regulating organs. I want to draw attention to the analogy with other diseases both as regards remissions and sex incidence, which have not been mentioned above. While there is no difference in sex incidence in rickets,  $\frac{2}{3}$  of the cases of spasmophilia in children and adults occur in males. Exactly the same relation is found in e.g. Addison's disease. In this last-mentioned disease the regulation of the Na- and Cl-content in the blood pursues the same irregular course. If this implies something more than a special instance of the tendency of the male sex to higher morbidity than the female, can always be discussed.

To conclude: Independent of the sex factor, lack of vitamin D disturbs the metabolism in rapidly growing organisms. This disturbance lowers very soon the phosphorus content in the blood and causes marked skeletal symptoms. We call this disturbance rickets. The lack of vitamin D aggravates the calcium regulation. The regulating organ, the parathyroids, are strained still more further. They are more or less regularly enlarged in rickets. If they are able to take care of the regulation fairly satisfactorily, no other symptoms than the rachitic ones are observed. But if they cannot uphold their function, a decrease in the calcium content in the blood *often* occurs, and its regulation in the blood is *always* disturbed, i.e. spasmophilic symptoms appear. How early the glands fail depends on constitutional factors. As in Addison's disease they fail more often in boys than in girls. They may do so before the development of any rachitic symptoms, but generally not until after this. In a very small number of cases they may fail even before the rachitic disturbance in metabolism has been diagnosed, i.e. in cases where the para-

thyroids are still more sensitive to the lack of sunshine than the metabolic organs.



FROM THE MATERNITY HOSPITAL PRO PATRIA, STOCKHOLM.  
HEAD: BJÖRN HOLMGREN, M. D.

## **Exanthema neonatorum from the Allergic Viewpoint, especially concerning the Influence of Orange and Vitamin C Supply to the Mother.**

By

**JUSTUS STRÖM.**

Most physicians with experience from pediatric practice are doubtlessly familiar with how intensely the skin often reacts with eruptions caused by foodstuffs. In their most typical form these exanthems appear as urticaria papulosa. In children with eczematous alterations of the skin, especially those of pruriginous character, it is furthermore almost a rule, that allergic factors play an eminent rôle.

During the first part of extrauterine life the skin is of course specially sensitive, as it then suddenly becomes exposed to all the new stimuli of the outer world. The change of the surrounding medium and its temperature cause the general reaction called erythema neonatorum. As a consequence hereof, but probably also due to the removal of foetal skin that remains to a greater or lesser extent from earlier stages of development, a desquamation results, exfoliatio neonatorum, in its most developed form called cutis testacea.

This general reaction and change of the skin is probably a contributing cause to the fact that the skin of the newborn exhibits changes of papulous and maculous character, caused by minor traumata in the course of nursing. These changes however are usually of short duration. Some superficial infections also play some part in this respect. Thus folliculitis is observed e.g. in the face if the child rubs or scratches itself, or around the umbilicus where the umbilical bandage has been applied.

But there is also a kind of skin eruption during the neonatal period that is usually distinctly different from those described above, by its appearance and its often more intense character. This later rather resembles the urticaria papulosa of old infants and small children. The eruption often consists of small oval, not seldom irregular rather strongly flushed skin areas, but little, and sometimes not at all raised above the skin level. Confluence of the spots to larger areas is not uncommon. In these spots one finds pin-head to rice-grain sized bright, and somewhat elevated papulae. There is often one such bright centre, seldom two or more. Sometimes it seems as if the single eruption had two or more bright papulae, but this is probably partially due to confluence.

According to my opinion, the similarity to urticaria papulosa is evident. In its course, the eruption also presents similarities to urticaria papulosa. The spots appear and disappear rather rapidly, and others are formed in new places. They are, however, to be found on the entire body, on the trunk as well as on the extremities, and in the face. There is no predilection as to the site.

The appearance of the exanthem, and its behaviour in other respects, suggests that it could be of allergic nature. What then could be the cause of the exanthem? The first explanation that presents itself is naturally that it should be caused by different drugs administered to the mother, and this is doubtlessly so in many cases. Many times it has also been explained in this way. However, one finds that the exanthem can appear in children, whose mothers never received drugs of any kind. In these latter cases it lies near at hand to regard the possible effect of some foodstuff.

As has been mentioned above exanthems in infants and small children often react unfavourably toward certain foodstuffs. On examining a number of my patient records from 1943—44, I have found that in 42 cases of eczematous eruptions of pronounced allergic character, oranges was one of the foodstuffs that most often had a deleterious effect on the exanthems (20 out of 42 reacted with distinct deterioration). As I subsequently observed

that exanthems in new born children became unusually numerous in winter and early spring, when oranges are available in the country, and that most of the mothers at the maternity hospital consumed often considerable amounts of oranges, I was inspired to investigate whether oranges could be of any importance in producing the exanthema of the new-born.

The foodstuffs that are apt to show unfavourable effects on exanthematous alterations of the skin, often belong to the ones rich in vitamin C, besides oranges e. g. tomatoes and many other vegetables, berries and fruit. Thus it also seemed of interest to find out if the pure vitamin substance, ascorbic acid, had any influence on the skin. The tests were therefore expanded to include this substance also.

#### *Test arrangement.*

In the maternity hospital Pro Patria there are two identical wards, each for 18 patients. In one of the wards the patients received 3 oranges a day, in the other they were prohibited to eat any at all. Close watch had to be kept to enforce this prohibition.

54 patients in all were allowed oranges in this fashion during their entire stay at the hospital (group A +), and 58 patients served as »non-orange» controls (group A —).

In the vitamin C tests each patient in one ward got two tablets of vitamin C (Astra), that is 100 mg. ascorbic acid pro die (group C +). 46 patients in all were provided with vitamin C, and 51 patients from the other ward served as controls (group C —).

The infants were examined every time they were looked after, notes were made concerning their skin, and any kind of eruption was carefully registered. The eruptions were placed under one of the following three headings: 1. Dots, 2. Spots, 3. Urticaria. Furthermore it was registered whether they were sparsely, moderately, or abundantly present, and for how long time they remained (1—2 days or more).

As I have already mentioned one can readily suppose that different drugs administered to the mother may produce exanthema. As both wards are identically arranged, the patient material and treatment the same, it may be assumed that the same kind of drugs were administered in both wards, and that consequently this possible source of error can be neglected. Some of the exanthems may of course have been caused by drugs, but it is only the difference that provides any proof.

Nevertheless I have examined the material from the viewpoint of administered drugs, and I have arrived at the following conclusion (table 1).

*Table 1.*

Test group	Number	Maxotyl cum codeini	Sulphathia- zole	Phenemal	Uterol
A +	54	41	3	12	8
A -	58	40	5	21	11
C +	46	41	6	16	15
C -	51	25	3	17	5

Thus all the drugs commonly prescribed at the maternity hospital can produce erythema, at any rate the salicylic acid derivative, phenemal and sulphathiazole. Usually, however, it has been cases of isolated prescriptions in small doses, and thus such an influence is improbable in most of the cases. One also finds that the drugs have been administered to a greater number of patients of group A - than of group A +. Thus this ought to have an unfavourable effect on the test results.

The number of cases with eruptions in the different groups are illustrated in table 2.

*Table 2.*

Percentage of children with eruptions.

Test group	Number	Percentage
A +	19 out of 54	35.2
A -	14 » » 58	24.1
C +	11 » » 46	23.9
C -	12 » » 51	23.5

The table shows that the percentage of exanthems is very even within the three groups A -, C +, and C -, in group A + on the other hand it is somewhat more than 11 % greater than in the rest. The orange group has thus shown the greatest percentage, but the difference between the latter and the control group is not conclusive.



Table 3.

Intensity of the exanthem	Duration in days	The type of exanthem											
		Dots				Spots				Urticaria			
		A+	A-	C+	C-	A+	A-	C+	C-	A+	A-	C+	C-
Sparse	1	1	4		4		6	1		4	1(+1)	2	1
	2	1	1	1	1					2			
	>2			1	1	1			1				
Moderate	1		1	1					1				
	2											1	
	>2	1	1	1					1	1		1	2
Abundant	1												
	2					2							
	>2					1		1		5		1	
Total		3	7	4	6	4	6	2	3	12	1(2)	5	3

However, if one proceeds to analyse the type of exanthem, one finds a rather characteristic difference (see table 3). Thus we find by far the greatest number of urticarial eruptions within group A+, no less than 12, of which 6 lasted for many days, and 5 of them were also characterized as abundant. Within the control group there are only two cases with sparse urticarial eruptions lasting one day. One of these cases has been put between brackets as it proved that the mother had been able to hide and consume some oranges the day before the exanthem appeared!

If one applies statistical calculation to the urticaria-material, one finds that within the group A+ urticaria was present in  $22.2 \pm 5.7\%$ , and within group A-, including the above mentioned »orange-case», in  $3.4 \pm 2.4\%$  of the cases. Thus the difference amounts to  $18.8 \pm 6.1\%$  which is significative. If the »orange-case» is excluded the percentage of the control group amounts to  $1.8 \pm 1.8\%$  and the difference to  $20.8 \pm 5.9\%$ .

No other certain differences can be established from the material. In the C vitamin series the results are very similar in

test and control groups. This of course suggests that other substances, and not the vitamin C, are the active ones.

The two cases with the strongest skin reactions will be related in order to illustrate the possible effect of the oranges still further. In general the patients do not stay long enough at the maternity hospital to allow an observation of the effect of the withdrawal and subsequent readministration of oranges, but in two cases this was possible to a certain extent.

Diary 421/1944. As early as on the second day urticarial eruptions began to show all over the body, especially on the trunk, combining to large areas in many places. The oranges were withdrawn. On the following day no change, on the second day an obvious decrease, and after two more days only spots were present, and these entirely disappeared on the eighth day. On the ninth day oranges were administered again. The following day spots on the chest, and the next day urticarial eruptions in the face. On this day the patient was sent home. — The mother had received one phenemal tablet (0.10) each night on the second to fourth day.

Diary 446/1944. On the twelfth day considerable urticarial eruptions had developed all over the body, most densely on the trunk and in the face. The oranges were then withdrawn. On the following day a considerable decrease and the second day no eruptions were found. — No drugs were administered.

However, in half of the cases of urticaria resembling skin reactions these have disappeared rather rapidly, and here one must presume that a rapid adaptation has taken place. The most pronounced cases, however, show that the tendency to react can remain for a considerable number of days. Doubtlessly this tendency to react is one characterizing the very first period of life, and which generally disappears later on. This disposition is probably closely allied to the properties of the skin of the new born, which I have mentioned above.

According to experience chocolate can also easily cause skin eruptions in sensitive individuals. As is well known the mothers in maternity hospitals often consume considerable quantities hereof. Therefore it may be of interest here to relate an instructive case.

Diary 109/45. In the evening on the second day after the child's birth, the mother consumed  $\frac{1}{4}$  kg. of chocolate. The following morning

the child exhibited a substantial eruption all over the body, most intense on the trunk, where the urticarial exanthems mostly joined to large areas with numerous small bright papulae. There were also numerous urticarial eruptions in the face and on the extremities. — Two days later the skin was once more free from eruptions. — After another two days, the mother was again allowed to consume  $\frac{1}{4}$  kg. of chocolate of the same kind. The next morning the child exhibited numerous papulae and spots in the face combining to larger areas on the cheeks. There were also a moderate number of spots on the trunk and quite a few urticarial eruptions and papulae on the legs. The following day only a few papulae remained on one of the cheeks.

During this time, no drugs nor any fruit had been given to the mother.

Thus this investigation shows that when considering exanthems in new-born children, one must bear in mind that these may be of allergic nature and that the cause must be sought not only in administered drugs but also in certain food-stuffs.

### Summary.

For many reasons the skin can be assumed to be sensitive to both external and internal stimuli during the neonatal period. Exanthems during this period are also rather common, and allergic factors presumably play an important part here, in any case in the urticaria-resembling varieties.

As oranges often proved to have a deteriorative effect on exanthems in infants and small children, and the suspicion had arisen that eruptions in infants also sometimes could be caused by the mother consuming oranges, tests were performed at the maternity hospital to elucidate this problem.

54 mothers received 3 oranges a day during their entire stay at the hospital, 58 served as controls. Urticarial eruptions in the new born children were present in 12 cases (22.2 %) of the former, but only in 2 cases (3.4 %) of the latter, the difference amounting to  $18.8 \pm 6.1$  %. Two graver cases are described in which the exanthems disappeared relatively soon on withdrawal of the oranges. In one of these latter cases the exanthem reappeared when oranges were allowed again. — In connection herewith another case is described in which a similar result was obtained with chocolate.

On administering vitamin C tablets à 100 mg ascorbic acid pro die to the mother, there was no difference between the test groups.

An examination concerning the administration of drugs to the mother during the test period revealed that in fewer cases of the orange group than in the control group, drugs had been administered that could be suspected of having caused eruptions.

Thus in exanthema neonatorum one has reason to investigate not only the administered drugs as a possible cause, but also the diet of the mother.

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FROM THE MEDICAL DEPARTMENT OF THE CHILDREN'S HOSPITAL AND  
THE GOTHENBURG MOTHER'S MILK CENTRE, SAHLGREN'S HOSPITAL,  
GOTHENBURG.

## Variations in the Fat Content of Collected Human Milk.

By

GERT v. SYDOW.

Of all the nutritive elements contained in human milk the milk-fat is that which shows the widest quantitative variations in different samples. A long series of different factors have been brought forward as capable of influencing the fat content and thereby contributing to this variability. Among these, those of practical importance and on a fairly firm footing may be said to be the *emptying phase* at which the specimen is taken, the *emptying technique* employed, the *time during the 24-hours cycle* at which the specimen is drawn, and the mother's *individual disposition*. With regard to the emptying phase LOWENFELD and associates, working on a large puerperal material, found that the difference between samples taken before and after the suckling of the infant during the same meal was always greater than 1 % of fat and could reach 5.8 % (3.64 % before nursing, 9.02 % after). The more powerful the pressure used for squeezing out the milk, the richer in fat did the milk become, and the milk poorest in fat was that which dripped out without pressure. For instance, if the first sample from one breast had dripped out of itself while the child was on the other side, and the other breast was pumped dry after the nursing, the fat content could rise from 0.60 % in the first sample to 6.45 % in the later one taken during the same meal. On the other hand, GÖLZ, who has also studied a large puerperal material, found considerably less difference between initial and final milk, on an average only 0.28 %, and never a higher difference than 1 %. He used, however, quite a

different emptying technique and considers, himself, that this is the cause of the difference in the results: in his material the whole quantity for the meal was drawn with a pump that operated all the time at about the same pressure, which prevented the more viscous fat from being as liable to be retarded in the milk-ducts as in the more natural emptying process. Respecting the daily variations most investigators have found that the fat content is highest in the middle of the day, with the maximum mostly at the 10 a. m. meal, and lowest at night, with the minimum at 10 p. m., 2 a. m. or 6 a. m. NIMS and her co-workers found that the difference between maximum and minimum varied during the 24-hour period between 14 % and 68 % of the lower value. As regards, lastly, the individual variability BELL, for instance, who on a large number of women completely emptied the one breast at the same time of the day, found on the fifth day of lactation a variation from a minimum of 0.9 % to a maximum of 8.2 % fat, on the ninth day from 1.6 % to 7.1 %, and in the fifth to sixth week of lactation from 1.3 to 7.6 %.

Less verified is the part played by such factors as the mother's age, number of the lactation, month of lactation, time of the year, mother's race, etc. Presumably these are also mainly of theoretical interest. Of more practical importance is the question of the connexion between *daily milk quantity* and fat content. On this point there are conflicting statements. Most investigators seem to have found that the fat content varies in inverse ratio to the quantity of milk. Recently, however, GÖLZ has found a higher fat content in hypergalactia than in hypogalactia, and SALMI has also arrived at a similar result. GÖLZ comments his results as follows: »La production abondante est donc un signe de bon fonctionnement du parenchyme qui produit aussi un lait nutritif, tandis qu'une production déficiente en quantité est due à un parenchyme défectueux qui ne produit également qu'une sécrétion de qualité déficitaire.»

Especially the question whether there is any connexion between *the mother's diet and state of nutrition* and the fat content of the breast milk, is of great practical interest. Numerous investigators have occupied themselves with this question, especially

in Germany after the first World War. On this point, too, different workers have come to different results. The majority appear to have come to the conclusion that the fat content of human milk had not demonstrably changed in the Germany of the distress period as compared with the pre-war values, but others found a distinct difference. Similarly, different results have been obtained respecting the possibility of increasing the fat content of the milk by an extra supply of fat or some other improvement in diet to the mother.

SALMI has recently published in this Journal another contribution in illumination of this question. He has discovered that the milk delivered during the years 1941—1942 to the Mother's Milk Centre in Helsingfors was on an average considerably poorer in fat than that delivered in 1939. The average for 1939 was 4.1 % of fat, while that for the years of war was only 3.1 %, or a diminution by 25 %. Primary data and statistical probability computations have not been furnished, but as the materials are large it is probable that the difference is statistically significant. The range of variation is large in both materials, but SALMI points out that the high fat values, above 5 % fat, occurred considerably more sparingly in the war-time material (in 4.6 %) than in the peace-time material (in 14.7 %). The other nutritive substances in the milk also showed lower values than in a small peace-time material studied earlier (YLPPÖ, 1928), but it may be remarked that this is very small, only 6 samples, and that the war-time material shows better agreement with an other, foreign, peace-time material.

SALMI's observation that even a milk collected from a large number of suppliers in the same community may vary considerably in fat content under certain conditions is however important. It would be still more important, however, if the material studied could be considered to be representative of all the human milk produced in the community during the same period, and the conclusion could thus be drawn that the breast milk which the infants of the town could get from their own mothers had also become, on an average, poorer in fat during the time of war. This conclusion does not seem to have been drawn by SALMI, but

it is one readily drawn by the reader. There is perhaps therefore reason to discuss *to what extent and under what conditions collected breast milk can be regarded as representative of the mother's milk in a community* so far as the fat content is concerned, and whether other factors than those dependent on the general level of nourishment would also be able to produce such a variation as was observed by SALMI.

The mothers supplying milk to a mother's milk centre naturally constitute a selected material in relation to the total nursing mothers in the community, in so far as they all have some degree of hypergalactia and consequently their milk production is probably always higher than the average the community can be assumed to have. If there is any correlation between the daily milk quantity and its fat content, an average of the fat content that has been obtained by determinations on milk from these high-milking mothers would not immediately be representative of the whole population. If it is correct that the fat content is inversely proportional to the amount of milk, the babies of the community would, on an average, get a milk richer in fat than that collected at the mother's milk centre. Conversely, if GÖLZ is right in his assumption that hypergalactic mothers also have fatter milk than hypogalactic or orthogalactic, the nursing would on an average get milk poorer in fat than that which the mother's milk centre delivers.

To this comes the fact that the high-milking suppliers to the mother's milk centre are naturally not everywhere and at all times selected with the same strictness. Differences in the demands for collected human milk, differences in the effectiveness of the propaganda, differences in the desire to help other mothers or in the desirableness of the benefits in the form of payment or increased food rations attached to the milk deliveries as well as other factors may, it is conceivable, sometimes cause a large number of mothers with only low-grade hypergalactia to be willing to supply milk, while under other conditions only mothers with a large and perhaps burdensome surplus consider it worth while being pumped out and delivering. The collected milk may therefore be unequally representative under different conditions,



and this inequality may be a source of error to be taken into account when drawing a comparison between different materials of collected human milk, e.g. between a peace-time and a war-time material.

This is probably, however, a point of less importance. No doubt it is considerably more important to decide whether the human milk that is delivered to the mother's milk centre is representative of the respective supplier's total production, or, failing this, whether it deviates in a tolerably regular way from what the mother's own child gets. It rests, of course, primarily upon this whether, from changes in the fat content of the collected milk, it will be possible to infer changes in the mother's milk taken as a whole.

Now, collected breast milk can be extracted in several ways. Some mothers empty their breasts completely after nursing when the child has not been able to suck them empty. In such cases it may be expected that the collected milk is richer in fat than the milk drawn by the child. Others pump out some of the milk before the child is nursed in order to prevent the baby from choking or the milk from running out of itself, during suckling, from the breast at which the baby is not feeding. In these cases it may be expected that the collected milk is poorer in fat than the milk imbibed by the child. A few mothers, whose children cannot suck themselves, empty their breasts completely by artificial means, after which the mother's milk centre is given what is over after the child has received its ration by bottle. In these cases, presumably, the fat content of the collected milk is generally identical with that drawn by the baby. Some milk is squeezed out by hand, other milk by means of a milk-pump of one design or the other. These different methods probably imply different degrees of emptying, and it may therefore be expected that the fat content varies a little according to the method by which the milk has been extracted. The poorest in fat is probably the milk that is allowed to run of its own accord down into a glass while the baby is feeding on the other side.

If a mother's milk centre has succeeded in getting its suppliers to adopt a uniform method for extracting their excess milk, it

might be possible to count upon a tolerably constant relation between the fat content of the collected milk and the fat content of the milk drawn by the mother's own child, so that from variations in the former it is possible to infer variations in the latter. At the Mother's Milk Centre in Gothenburg, which is now one year old, we have so far not made any attempts in this direction. As a rule we have allowed the suppliers to continue with the system they have found to suit them, and have intervened only to rectify hygienic mismanagement or methods that entail manifest disadvantages to the supplier herself or her baby. During the last month I have tried to get into contact with all mothers who are now supplying milk to the Centre and have questioned them very searchingly as to how they have acted in order to recover their surplus milk during the time they have been delivering to the Centre. The particulars obtained have then been compared with the fat percentage found in the samples (since the summer of 1944 this has been regularly determined once a week on each supplier's milk according to Gerber's method). By this means I have obtained a material that will serve to illuminate the effect of the different methods on the fat content of the collected milk. The material is tabulated below.

Altogether, the fat content has been determined on 1004 samples from 165 suppliers (*Material a* in the Table). 65 of these were continuing to deliver milk at the time of the investigation. Of these, complete details as to the emptying technique could be obtained in 49 cases (*Material b*). 14 of the mothers had emptied one or both sides *after* the infant's meal (*Material c*). Four of these had collected, in addition, small quantities that had spontaneously run from the other breast during suckling. Most of these 14 had solely or mainly used a hand-pump, only three mothers had squeezed the milk out with the hands alone. 14 mothers had, mainly, pumped the milk out *before* the baby's meal (*Material d*), two of them with a water-suction pump, nine with a hand-pump, three by hand. Practically all these, however, had also squeezed out small amounts after the meal or had collected small quantities of milk that had been discharged of itself from

the breast not in service at the moment. Four of the mothers had pumped out before the morning meal or before the two first meals; at the other meals they had squeezed out a few drops after the meal if there had been any left. 10 mothers had exclusively or chiefly collected milk that had *run of its own accord from the other breast* while the baby was feeding. Two of these had helped a little with a hand-pump against the nipple while the infant was sucking, and one had used a cupping glass for the purpose. Three of these mothers had in addition drawn a little milk with a hand-pump before and after the meals, one only before and one only after, from the breast at which the child had fed or should feed. To this material three mothers have also been referred who for the most part had only pumped from *the breast at which the baby was not feeding*, either by hand or by hand-pump. Hence this material amounts to 13 cases (*Material e*). *Material f* comprises two mothers who had pumped out *all their milk* by hand-pump or water-suction pump and who, after giving their own child its ration from the pumped-out milk, had delivered the rest to the Milk Centre, and three mothers who had drained out and delivered the *whole evening meal*, by hand or by hand-pump, after the baby had been weaned from its last meal. Lastly, grouped as *Material g*, there are 6 mothers who had applied various methods indiscriminately without any one method having noticeably dominated over the others. The reason the total number of donors in the groups *c* to *g*, inclusively, exceeds that of the whole material is that some mothers have changed their emptying technique during the period of delivery and have therefore belonged first to one group for a time and then to another group.

	No. of Donors	No. of Samples	Average Daily Quant. deliv.	Average Fat Content
<i>a</i> (whole material) . . . .	165	1004		3.10 $\pm$ 0.03
<i>b</i> (investigated material) .	49	427	285.7 $\pm$ 19.2	3.24 $\pm$ 0.05
<i>c</i> (after nursing) . . . . .	14	136	260.5 $\pm$ 25.9	3.56 $\pm$ 0.09
<i>d</i> (before nursing) . . . . .	14	123	280.3 $\pm$ 39.9	3.08 $\pm$ 0.12
<i>e</i> (spontaneous discharge) .	13	102	300.8 $\pm$ 56.2	2.89 $\pm$ 0.05
<i>f</i> (milked dry) . . . . .	5	30	254.2 $\pm$ 61.1	3.65 $\pm$ 0.16
<i>g</i> (mixed technique) . . . .	6	34	351.0 $\pm$ 61.5	3.44 $\pm$ 0.20

It will be seen that the figures in the table agree well with the observations previously made respecting the influence of the emptying technique on the fat content. Milk extracted by pumping after suckling shows a higher average fat content than that extracted before suckling, and spontaneously discharged milk exhibits the lowest fat content of all. A notable feature is that in those cases in which all milk was drawn by artificial means, or in which certain meals were entirely drawn by such means (Material *f*), the fat content was the very highest (the diff. *c-f* is, however, not statistically verified), whereas in those cases in which that breast was milked dry at which the baby was not feeding at the moment the milk had as low a fat content as spontaneously discharged milk. The reason is presumably to be sought in the unequal energy applied in squeezing out the last drops in the two groups. Statistically significant differences were found in the following cases:

<i>a-c</i> : Diff. = $-0.46 \pm 0.09$	<i>c-d</i> : Diff. = $0.58 \pm 0.15$
<i>a-e</i> : Diff. = $0.21 \pm 0.06$	<i>c-e</i> : Diff. = $0.67 \pm 0.10$
<i>a-f</i> : Diff. = $-0.55 \pm 0.16$	<i>d-f</i> : Diff. = $-0.62 \pm 0.20$
<i>b-c</i> : Diff. = $-0.32 \pm 0.10$	<i>e-f</i> : Diff. = $-0.76 \pm 0.17$
<i>b-e</i> : Diff. = $0.37 \pm 0.07$	

Between materials *a* and *b* the difference is not verified though probable (Diff. =  $-0.14 \pm 0.06$ ). The same applies to the difference between *b* and *f* as well as *e* and *g*. In all the other cases the difference is less than twice its standard error. It may therefore be regarded as established that milk pumped out after suckling or milk from breasts completely emptied by artificial means has a higher average fat content than collected breast milk in general, and that milk which runs of its own accord from the breast or which has been emptied from the breast at which the infant is not feeding has a lower average fat content than collected human milk in general. On the other hand, in this material it has not been possible to establish any difference in fat content between milk that has been pumped out before the baby is suckled and collected breast milk in general.

Judging from the data given in the Table, the average daily quantity of milk delivered to the Milk Centre appears, on the

whole, to vary in such manner that the groups with the highest fat content have the lowest daily quantity, and conversely. The differences, however, are in no case statistically significant or probable, and they cannot therefore be assigned any significance whatever.

Some guidance in deciding the question whether the collected milk is representative of the supplier's total milk production might conceivably also be obtained from *the infant's increase in weight*. In those cases of my material in which a sufficient number of weight data could be obtained it was found that the average weight increase per month of the children whose mothers had given milk recovered *after* nursing was  $765 \pm 62$  gm., of the babies whose mothers had delivered milk extracted *before* nursing  $866 \pm 42$  gm., and of the babies whose mothers had supplied *spontaneously discharged milk*  $636 \pm 97$  gm. The differences are not significant or probable. In a material of children of this kind, however, birth-weights as well as age vary considerably during the period of observation, which makes the material rather unsuitable for comparisons. Moreover, any variations occurring in the fat content of the milk in the different groups may very well be compensated for by variations in the quantity of milk consumed by the babies, concerning which nothing is known. This method of approach is consequently not practicable, unless there is available a sufficient material of babies of about the same size for which the increase in weight has been determined during a given period of age, e. g. during the second month of life, and for which the quantities of the meals have also been fixed by weighing.

The probable difference that exists between the whole material and the investigated material (Materials *a* and *b*) seems most likely to depend on differences in the proportions of milk extracted by one or the other method. Of course, the possibility of other factors having been at work, e. g. seasonal variations, cannot be excluded. Whether different emptying techniques could account for the difference between Salmi's peace-time material and his war-time material seems, on the other hand, to be considerably

more dubious. So great a difference as appears between these two materials does not exist between any of the groups in my material. To this it may be objected that the different groups in my material have not been graded out and that therefore the donors in, for instance, Material *d* have by no means supplied only milk that had been pumped out before suckling but, as a rule, also milk recovered in some other way, and that the differences between the groups would probably have been larger if these had contained only graded cases. However, such graded cases are doubtless rarely dominant in practice — they would be so, for instance, if in times of want the opinion spread among the donors that it was now a question of letting, first and foremost, their own children have the most nourishing portion of the milk, i. e. that last pumped out. A sudden realization of this state of things has led in some of my cases to an alteration of the emptying technique and a changed fat content of the milk drawn.

There are two small materials in SALMI's paper, one from peace-time and one from war-time (pp. 2—3 and p. 22 respectively), which are well specified and appear to be well comparable. In the former case I have computed the average fat content at  $3.11 \pm 0.18$  % (under the admittedly not quite accurate assumption that the milk quantities for each meal given by the same mother were the same size). In the latter case the average fat content is  $3.04 \pm 0.08$  %. The breast had been completely emptied in both cases one or more times the same day. The difference between the two materials is  $0.07 \pm 0.20$  %, thus not significant. Of course, this does not in any way rule out the possibility that a larger material, in which, as here, the milk has been recovered in a tolerably uniform manner, might show a significant difference between peace-time and war-time, but it may nevertheless be regarded as suggesting that other factors than supply of nourishment have also contributed to the great difference between the peace-time and war-time values in SALMI's material. It cannot be immediately postulated that these factors must have been operative in the same degree or in the same direction on the fat content of the total milk production of the mothers as in the collected portion.

Probably the deterioration in the supply of food has contributed to the fall in the fat content during the war, but this cannot be considered to be proved by the material published by SALMI. A later opportunity will possibly offer of supplementing his material so that increased clarity can be gained in this matter. In that case it would be urgent for this to be done, as the question is a very important one.

### Summary.

The fat content of collected human milk surplus is not representative under all conditions of the mother's milk fed to the babies of the suppliers to the Milk Centre, and variations in the fat content of the collected milk need not imply that the milk which the baby gets varies in the same way. Different emptying techniques (e. g. extraction at different emptying phases) may yield milk that has considerably different fat contents, and this would if anything imply that the fat content of the rest of the milk, which the baby draws, varies in the opposite direction.

If, for instance, it is wished to decide whether an altered level of nutrition in a community has had an effect on the fat content of human milk, a material should preferably be procured that is fully representative of the total production of the mothers studied, e. g. the whole daily milk production from a number of mothers, and, best of all, from mothers who, among other things in respect of milk quantity also, are representative of the nursing mothers of the community. At any rate, when comparisons are made, it must be seen that the different milks have been extracted by a uniform technique and can thus be presumed to deviate in the same way from the total production of the donor mothers as regards fat content.

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### Supplement to proof.

In May 1945 I was given the opportunity of organising a hospital for 45 Polish mothers with their babies just arrived from the concentration camp at Ravensbrück in Germany. The babies were all between 15 days and 2 1/2 months old on arrival. The mothers had been brought to Germany 6—9 months before delivery and set to do heavy physical labour at munition factories etc., till the last two or three months of pregnancy when they were transferred to Ravensbrück. Their daily ration was said to have consisted of about 300 grms. of black bread and turnip soup. Some of them stated that they had exchanged their bread ration for pieces of cloth to make clothes for their babies. The babies had been reared at the breast with or without a supplement of "schleim" of unknown composition, distributed from the camp kitchen. The mortality among the infants and among the mothers too seems to have been very high. A few women who had lost their own children were found to be suckling babies who were not their own, but whose mothers had died. Other women who had also lost their own children joined the group and acted as wet-nurses. On arrival in Sweden the children were in very bad condition, many of them extremely thin, showing signs of atrophy and exhaustion and looking like infants with severe pyloric stenosis. Gradually most of the children have attained a rather good condition but a number have shown themselves to be infected with tuberculosis, the not unnatural consequence of their journey. Most of the mothers too whose condition on arrival was very poor have begun to flourish and put on flesh.

By courtesy of Dr. BIRGER WAHLSTRÖM, the medical officer in charge of the hospital, and later of his successor, Dr. HEDVIG RYDÉN, I had the opportunity of examining milk samples from 10 of these mothers, taken 11—15 days after they had been given more nourishing food on their journey here, and two months later new samples from 9 of the same women. The samples were extracted by completely emptying the breasts by the hand at 2 p.m. and after stirring, about 20 cc. of the milk so extracted was sent for examination. The quantities of milk obtained varied at the first examination between 20 and 100 grms. and on the second, between 30 and 175 grms.

At the first examination the fat content was in 9 out of 10 cases over 4 % and in the tenth case 2.5 %. At the second examination the fat content in 7 out of 9 cases was more than 4 % and in 2 cases more than 5 %. The highest value obtained was 5.5 % and the lowest, 2.5 %. In nearly all samples from both examinations the fat content was thus clearly higher than the average of both the total material and the different groups examined at our mother's milk centre. Only one sample in each of the materials had fat content below the average, all the others were considerably higher.

The explanation can of course be found in a number of different circumstances. One can bear in mind the difference in race between the Polish and Swedish mothers, and also the fact that when the first samples were taken, the mothers had already been enjoying an adequate diet for a short time. It may also be pointed out that most of the samples in this material were derived from hypogalactic mothers as against hypergalactic mothers who supply milk to a mother's milk centre. It is of course evident that the material collected is far too small to permit of any safe conclusions. The noticeably high values however appear to contradict Salmis contention that undernourishment lowers the nutritive value of mother's milk.

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## **Studies on the Absorption of Iron.**

### **I. Absorption of Iron from the Stomach.**

By

**BO VAHLQUIST, GÖSTA NEANDER and EBBA NEANDER.**

During the past ten years much has been learned of several important aspects of the metabolism of iron. Serum iron analysis and experiments with radioactive iron have been of decisive importance in this connection. One of the most interesting discoveries has been that the organism can excrete only insignificant quantities of iron and that the iron balance is mainly determined by the extent of the absorption (HAHN *et al.*, 1939 b).

The absorption of iron is regulated by the needs of the body. Normal individuals absorb iron if it is administered in suitable form and adequate quantity, but in those suffering from iron deficiency, the absorption of iron occurs on a much larger scale under otherwise similar conditions (HAHN *et al.*, 1939 a; BALFOUR *et al.*, 1942).

It has long been believed that the absorption of iron takes place principally in the duodenum and the uppermost part of the jejunum. Experiments in which iron salt was introduced through an intestinal tube several meters down in the small intestine have shown, however, that this part of the intestine is also capable of absorbing iron (WALDENSTRÖM, 1940).

Several years ago DELHOUGNE (1931) came to the conclusion on the basis of animal experiments that under certain circumstances iron can be absorbed from the stomach also. No mention of these results has been made in the clinical literature. However, the question of whether iron is absorbed from the stomach, especially the human stomach, is of considerable theoretical as well as practical interest.

Serum iron analysis provides a relatively simple method of establishing when absorption of iron takes place. The results presented herein concerning the absorption of iron from the stomach in the white rabbit and in man are based on an analysis of the serum iron curve following iron tolerance test in the presence of artificial stenosis of the pylorus.

#### *Methods and Results.*

The serum iron was analyzed according to the HEILMEYER-PLÖTNER method, modified by VAHLQUIST (1941).

*Experiments on white rabbits.* The animals were first starved for 12 to 24 hours. Laparotomy was then done, the animals being anesthetized with Numal (Roche) — 0.5 Ml per kilogram of body-weight intravenously. The pylorus was occluded with Péan's forceps or a ligature. 100 mg of iron in the form of Guttafer (Ferrosan) was administered. Successive samples of 3 to 4 Ml of blood were taken from the auricular vein or the vena cava. The stenosis was relieved and the blood tests were continued.

The results of the iron tolerance tests are shown in Table 1 and Figure 1.

*Experiments in man.* The experiments were conducted in the morning with the subjects fasting. Stenosis of the pylorus was accomplished by means of a tube with an inflatable rubber bag according to HALLÉN's (1943) method. 194 mg of iron (1 Gm of iron lactate) suspended in 20 Ml of water was passed into the stomach through a tube. A series of tests were made at fifteen-minute intervals. After 45 minutes had passed 0.5 mg of histamine was given subcutaneously. After 90 minutes the stenosis was relieved, at the same time as 97 mg of iron (0.5 Gm of iron lactate) was injected directly into the duodenum. The last test was made 150 minutes after the stenosis was instituted.<sup>1</sup>

The above experiment was made on three persons, as follows:

*Experiment 1.* K. E., a woman of 22 years, was healthy, with blood levels somewhat lower than normal; Hb., 11 Gm percent; red blood count, 3 500 000. The experiment was made on February 21, 1945.

<sup>1</sup> The authors are greatly acknowledged to Dr. LARS HALLÉN and nurse MAJ-BRITT ROOSTEN for valuable help in performing these experiments.

Table 1.

Serum iron values in iron tolerance tests on rabbits submitted to artificial stenosis of the pylorus.

Animal No.	Weight kg.	Initial serum iron value $\gamma$ -%	Rise in serum iron, $\gamma$ -%				Notes
			0'	15'	30'	43'-56'	
26	2.4	117		+76	+147	53': +188	15-min. test interpolated (Fig. 1). »30-min. test» made after 32 min.
27	2.2	208		—	+120	56': +200	»30-min. test» made after 37 min.
34	2.4	176		—	+40	43': +141	30- & 43-min. tests made on porta blood. Animal received 10 g glucose together with iron.
90	2.3	230		+8	+61	—	
91	3.0	229		+37	+131	—	

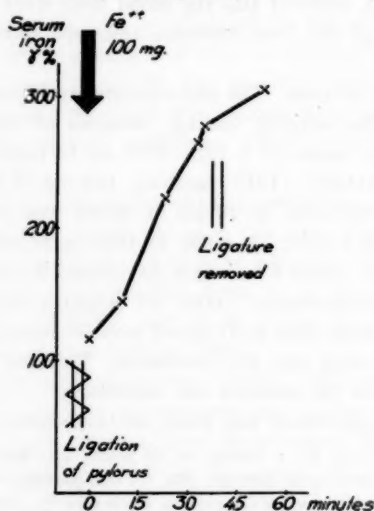


Fig. 1. Serum iron curve following iron tolerance test with artificial stenosis. Experiment on rabbit No. 26.

Table 2.

Serum iron levels during iron tolerance tests in persons submitted to artificial stenosis of the pylorus.

Case		Initial serum iron value γ-%	Rise in serum iron γ-%								
			0'	15'	30'	45'	46'	60'	90'	91'	150'
K. E.	Pyloric stenosis	98	Fe <sup>++</sup> 194 mg.	+ 1	+28	+42	Histamine 0.5 mg.	+67	+125	Stenosis relieved Fe <sup>++</sup> 97 mg	+232
S. F.		46		+ 6	+26	+24		+44	+ 49		+ 86
T. L.		67		-10	- 5	+28		+36	+ 31		+117

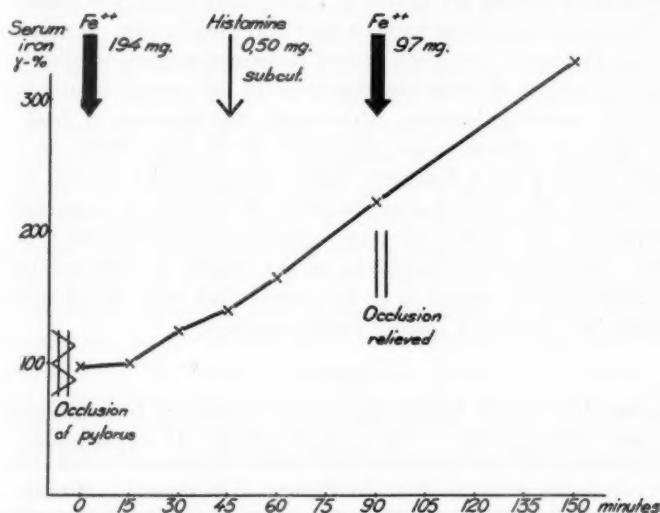


Fig. 2. Serum iron curve following iron tolerance test with artificial stenosis. Experiment 1 (a woman).

*Experiment 2.* S. F., a man of 26 years, was recovering from hemorrhagic anemia following traumatic amputation of a leg. He had received transfusions and iron therapy. The following blood values were noted: January 8, 1945: Hb., 8.5 Gm percent; red blood count, 2 900 000. February 8: Hb., 12.5 Gm percent; red blood count, 4 200 000. The experiment was made on February 15.

*Experiment 3.* T. L., a man of 50 years, had pernicious anemia in

remission. The following blood values were noted: February 3, 1945: Hb., 4.8 Gm percent; red blood count, 1 200 000; serum iron, 245  $\gamma$  percent. From February 7 to 9, the patient received 12 Ml of Pernaemon forte intramuscularly in doses of 4 Ml. Blood values on February 23 Hb., 8.7 Gm percent; red blood count, 2 800 000; serum iron 67  $\gamma$  percent. The experiment was made on February 23.

The results of the iron tolerance tests are shown in Table 2 and Figure 2.

### Discussion.

The stenosis experiments were first performed on rabbits. Even after fasting for twelve to twenty-four hours, the contents of the stomachs of these animals were still considerable. Ignorance of this fact has undoubtedly caused numerous workers to misinterpret the results of other experiments with the peroral administration of various substances. Presumably the presence of food in the stomach influences the absorption of the iron. Many of our experiments proved, however (Table 3), that under normal conditions the 100 mg of iron administered gave rise to a considerable increase in the serum iron level, sometimes exceeding 300  $\gamma$  percent. The individual variations in the results of tolerance tests on these animals appear to be no greater than those found in the serum iron curves of fasting human subjects.

Table 3.

Serum iron levels before and in the course of iron tolerance tests (100 mg.  $\text{Fe}^{++}$ ) on normal rabbits. 17 experiments.

		Minimum	Maximum	Median
1.	Initial value, $\gamma$ % . . .	99	304	193
2.	Rise after iron administration, $\gamma$ % . . . .	+56	+361	+132
3.	Minutes elapsed between 1 and 2 . . . . .	26	60	35

As shown in Table 1, a distinct increase in the serum iron was observed in all the stenosis experiments. In two of the experiments it was moderate (No. 34, +40  $\gamma$  percent; No. 90,

+ 61  $\gamma$  percent). In the remaining three, the serum iron increase was just as pronounced after 30 minutes (No. 26, + 147  $\gamma$  percent; No. 27, + 120  $\gamma$  percent; No. 91, + 131  $\gamma$  percent) as in many of the controls in which the pylorus passage was free and corresponded well with the median value noted in these experiments, i. e. 132  $\gamma$  percent, after an average of 35 minutes.

In two of the experiments (Nos. 26 and 91), the serum iron level had risen appreciably only 10 to 15 minutes after the administration of the iron. The same rapid rise had already been noted in the control experiments and, in fact, was what led us to investigate whether iron is absorbed from the stomach also.

No conclusions as to the amount of iron absorbed can be drawn directly from the serum iron curve, but the results of these tolerance tests show that absorption from the stomach really does take place. Nor do the curves suggest that the absorption occurred more rapidly after the stenosis had been relieved.

What, if any, are the sources of error in the method? In several experiments the fact that neither Numal as a narcosis, the operative intervention, nor the stenosis had any appreciable effect on the serum iron value was established. The amount of iron administered, or about 40 mg per kilogram of body-weight, was considerable. However, there is scarcely reason to believe that it injured the gastric mucosa, especially in the case of the well-filled rabbit stomachs. Nor did histologic examination of the mucosa in two cases show any morphologic changes. Occlusion of the pylorus with a Péan's forceps or a ligature, applied under the dissected vessels at the pylorus, presumably influenced the gastric peristalsis and may even have had an unfavourable effect on the circulation of blood in the stomach. However, both these sources of error would reasonably be expected to have led to a smaller increase in the serum iron value than otherwise.

The positive results of the animal experiments led us to make a similar investigation in man also. Stenosis at the desired level can be accomplished with little discomfort to the patient by means of a gastro-intestinal tube equipped with an inflatable rubber bag (ABBOTT, 1942; HALLÉN, 1943).

Iron tolerance tests in normal persons usually give a distinct,

although varying increase in the serum iron value. Chosen to act as subjects were a student nurse with somewhat low blood values, in whom several previous tolerance tests had shown a pronounced rise in serum iron, and a patient recovering from hemorrhagic anemia, in whom similar conditions could be expected *a priori*. In addition, we chose a patient with histamine-refractory achylia, a case of pernicious anemia in remission. The amount of iron administered, i. e. 1 Gm of iron lactate (= 194 mg of  $\text{Fe}^{++}$ ), was double the dose given by one of us in earlier tolerance tests (VAHLQUIST, 1944).

The results of the experiments given in Table 2 and Figure 2 seem to us to show that iron can be absorbed from the human stomach also. The rise in the serum iron value observed in Experiment 1 occurred at about the same rate before and after the relief of the stenosis. The rise recorded after 90 minutes was probably somewhat less than in previous control experiments on the same person, particularly in view of the larger dose of iron now given. However, the figure 125  $\gamma$  percent is well-founded. In the other two experiments the increases were not so large, but nevertheless showed such a definite trend that the possibility of »spontaneous» variations could be disregarded. Nor was there much chance of a daily rhythm (VAHLQUIST, 1941), making itself felt during the relatively short period the experiments lasted; in any case, it probably would have led to a decrease in the serum iron.

Questions of essential importance, of course, are whether the stenosis was fully effective and was applied at the right level of the pylorus. The method we used, which has been followed for several years by HALLÉN, appears to guarantee that these two conditions are fulfilled. After the stenosis had been accomplished, the patients remained in the left lateral position for the duration of the experiment.

The experiments reveal primarily that iron can be absorbed from the human stomach also. They also show that absorption of iron in the form administered occurs regardless of the hydrochloric acid content of the stomach. The injection of histamine had no appreciable effect on the serum iron curves in Experiments

1 and 2 (K. E. and S. F.), and a rise in the serum iron level was also noted in Experiment 3 (T. L.), in which the patient had histamine-refractory achylia.

Judging by the appearance of the serum iron curves, the absorption of iron in all three experiments in man did not set in until a certain latent period had elapsed, and in all the 15-minute tests the serum iron level was unchanged. In two of the animal experiments, however, tests made ten or fifteen minutes after administration of the iron showed a definite rise of the serum iron level (No. 26, +28  $\gamma$  percent; No. 91, +37  $\gamma$  percent). After thirty minutes had passed, Experiments 1 and 2 showed a distinct increase, but in Experiment 3, in which the patient had a pernicious anemia in remission, no rise was recorded until forty-five minutes had passed.

As far as we can discover, no experiments to study the absorption of iron from the human stomach have hitherto been made. On the whole, our knowledge of the absorptive ability of the stomach, particularly the human stomach, is still far from complete. With regard to glucose, however, it seems now to have been definitely established that when administered in hypertonic solution it can be absorbed from the human stomach (SHAY *et al.*, 1939; WARREN *et al.*, 1940). In animal experiments TEORELL (1939) observed absorption of acids, bicarbonate, sodium sulfate etc.

Of particular interest in this connection are the animal experiments conducted by DELHOUGNE. He studied dogs with duodenal fistulas made »kurz hinter dem Magenausgang». The closure of the pylorus was regulated by moistening the duodenal mucosa with hydrochloric acid or ammonia. The absorption was calculated as the difference between the substance administered through a gastric tube and that recovered from the fistula. DELHOUGNE summarized his results as follows (p. 136): »Monosen, Aminosäuren, Alkohol, Eisen, Jod und verschiedene andere Arzneimittel können zum grossen Teil von der Magenschleimhaut resorbiert werden. Die Resorption tritt nur dann ein, wenn die betreffenden Stoffe länger im Magen verweilen... Die Resorption erfolgt wahrscheinlich im Fundus. Resektion der Pylorus-gegend



hat jedenfalls auf die Resorptionsgrösse der Magenschleimhaut keinen Einfluss.» Absorption set in sooner after cauterization of the mucosa with alcohol, but the final result noted after the passage of three to four hours did not differ from the other experiments.

With iron, administered in the form of iron lactate, the results in the control experiments in which the mucosa was not cauterized were as follows: Quantity of iron: 189 mg; absorbed after one hour, 5 mg; two hours, 10 mg; three hours, 21 mg; four hours, 33 mg. The final result thus showed absorption of 17 percent of the relatively large amount of iron administered. It may be objected that not only absorption, but adsorption also may have influenced the result.

Radioactive iron is exceedingly well suited to studies on the absorption of iron. A paper by HAHN and coworkers (September 1943), which did not come to our attention until after our experiments had been completed, reports an experiment on a dog with a gastric pouch that had been anemized by hemorrhage. Of a dose of 188 mg of radioactive iron, 10.4 percent was absorbed during the course of two hours. HAHN wrote: »This is as much and possibly more than the expected absorption of radio-iron in the same animal under these conditions of iron depletion and anemia even with an intact gastrointestinal tract.»

The results of animal experiments cannot, of course, be applied directly to human beings. In a study to demonstrate the gastric absorption of glucose, SHAY *et al.* (1939) wrote that their experiments »clearly show that experimental results obtained by studying absorption and dilution in isolated intestinal loops cannot be compared with results obtained from studying intact gastrointestinal segments». Our present experiments, however, all indicate that iron can be absorbed from the human stomach also. It is then clear that the gastrointestinal tract, from the stomach to deep down in the small intestine, is able to absorb iron.

The absorptive capacity of the different segments depends *inter alia* on the following factors: 1) the form taken by the iron when it is in contact with the different segments, 2) the length of time the iron is in contact with the mucosa, and 3) the blood supply of the

mucosa. Analysis of these factors is not easy. The iron consumed in food and the iron administered in therapeutic doses are not directly comparable. The evacuation of the stomach varies considerably under normal conditions and even more so in disease. Precipitate evacuation has been observed in certain cases of iron-deficiency anemia. However, it can probably be said that the acid reaction of the gastric contents is more favourable to the absorption of iron than the neutral reaction in the intestines. After an average meal with or without extra iron, the one- to three-hour period in the stomach should suffice both for the splitting of available iron and for the absorption of iron.

### Summary.

By studying the serum iron curve following iron tolerance tests in individuals submitted to artificial stenosis of the pylorus, it was established that iron is absorbed from the stomach, in animals as well as in man.

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## **Breast-Milk Consumption of Healthy Full-Term Infants.**

By

**ARVID WALLGREN.**

A very common information as to the quantities of breast-milk consumed by the infant found in text-books and manuals of pediatrics is that breast-milk consumption varies proportional to increase in body weight in such a manner, that the quantity of milk consumed during the first quarter of the first year of life is equivalent to one sixth, during the second quarter to one seventh, and during the third quarter to from one eighth to one ninth of body-weight. According to the same sources of information the quantities of breast-milk required can be calculated on the basis of the data as to the infant's caloric requirement per kg body-weight at different ages. During the first quarter it is supposed to require from 110 to 100 calories per kg, during the second quarter 90 calories per kg. As a rule, the breast-milk is reported to be equivalent to 700 calories per liter. These reports are based on investigations made during the end of the last century on a material that, as a rule, was rather limited, and statistically not always fully representative. Besides these investigations generally disregard the variance in the individual requirements — the existence of this variance from infant to infant is definitely recognized — and no statistical analysis of the results was made.

The experienced pediatrician is fully aware of the fact that it is impossible to determine in advance the required quantities of milk in proportion to age and body-weight. In practice, however, this rule is frequently applied. In this connection a method should be recalled, which is frequently used in mixed feeding.

According to this method the quantity of breast-milk consumed by the infant is compared with a known standard figure. If the consumption is below this figure the deficiency is compensated with a corresponding quantity of artificial diet. Obviously, neither children's nurses nor physicians seem to have realized that it is mere guessing if it is assumed that a certain child's requirement of breast-milk corresponds exactly to the mean value of infants in general.

In the case of a healthy child that is developing normally, it is, as a rule, not necessary to pay special attention to the quantities of breast-milk consumed. In these cases the quantity of milk consumed will be sufficient anyhow, irrespective of its absolute volume. It is justifiable to assume that every healthy and well developed infant fed on breast-milk alone, get as much milk as it really requires. It would, however, be a matter of theoretical as well as of practical interest to ascertain 1) the quantities of breast-milk which the healthy infant requires, and 2) to get information about the limits of variations of the normal amounts of milk. It is a most surprising fact that pediatric literature contain very little data on this question. The object of the present investigation is to fill this gap in our knowledge of the physiology of the infant.

The investigations as to the quantities of milk consumed by the infant were made on children who were controlled by an Infant Welfare Centre directed by the author. The children were nursed and brought up in their respective homes by their mothers who were non-professional women. All the children lived under controlled physiological conditions. They belonged to various socioeconomic groups of population — this is usually the case with children in charge of the Infant Welfare Centres in Sweden — and when selecting them for purposes of investigation the only factors which were taken into consideration were that the mother was able to check her baby's weight as well as the quantities of milk consumed, and that her reliability was unquestionable. During the years the reported investigations were in progress, the children who were selected for examination, had to present the following prerequisites:

1) that they were full-termed children and had been and were fed solely on their mother's milk five times a day at intervals of 4 hours, 2) that there was a negative history of nutritional disturbances, 3) that their development had in every respect taken a normal course, 4) that their health was satisfactory and that they had not manifested any symptoms of digestive troubles, 5) that the child's mother was and had been healthy, 6) that the mother's diet and way of living had been controlled and found to be adequate and impeccable. The investigations were made before the present war-time conditions.

The children came under the control of the Infant Welfare Centre subsequent to the neonatal period. The youngest children who were investigated were aged 2 weeks. Since weaning, as a rule, is started soon after the child has attained its sixth month, the oldest child subjected to examination had attained the age of 6 months. For the purpose of facilitating statistical analysis the investigations were made at exactly the point of time corresponding to the reported ages. The results obtained on the groups of age comprising infants aged 2, 3, 4 and 6 weeks, as well as on the groups of children aged, 2, 3, 4, and 6 months were statistically analysed.

Milk consumption was calculated by checking the child's weight previous and subsequent to each meal. Increase in weight produced by the meal was recorded, and was considered as quantity of milk consumed. The sum of the weights of milk corresponding to the 5 meals per day was considered to express the volume of milk consumed.

Since it is well known that the quantity of breast-milk consumed may vary considerably not only at each meal, but even from one day to the other, the quantities of milk consumed within each group of age were determined in duplicate on two subsequent days. Milk consumption in proportion to age and weight was determined on the basis of the mean value of these duplicate determinations.

When comparing the results obtained in the course of two subsequent test-days it turned out that two thirds of the infants

showed a variance below 5 per cent. The greatest variance observed was equivalent to 39 per cent.

The home of each child was repeatedly inspected by the visiting nurse of the Centre. Not until the latter had convinced herself that the mother really was able to weigh her baby and check the weight with necessary accuracy were the mother's information as to the quantities of milk consumed, considered fully reliable. If there was anything of note in regard to the reported milk consumption the nurse made control determinations. The babies were weighed on ordinary infant's scales.

More than one hundred determinations were made in duplicate on each group of age though not each single child was examined at all selected ages. In the majority of cases the determinations were made on two or three occasions only. Most of these instances belonged to the age-group comprising the oldest children. Since only children who had previously been in good health, were included in the investigation, the collection of a sufficiently large number of determinations on children having attained the oldest age in question, encountered difficulty. Frequently, the children suffered from some disease or some other kind of disturbances at the age of a few months, and could, therefore, later not be considered as normal children. Some other children had to be excluded, because of some illness of the mother or because, for some reason or other, they were no longer fed on breast-milk alone, when they had attained the required age. At a certain stage of the present investigation when an adequate number of determinations in regard to the groups of age comprising the youngest children was already available, the number of determinations made on the oldest children, was not yet sufficiently large. This gap in the information as to the volume of milk consumption within these groups of ages was filled by investigating separately any individual child whose condition was considered to be adequate. Any child who, at the time when the determinations were made, was suspected of not consuming the quantity of milk corresponding to or less than its actual requirement, was excluded. Thus mothers presenting hypogalactia were definitely excluded.

The milk consumption was determined in 363 children (183 boys and 180 girls). Birth weight of all the children was at least 3 000 g. In 146 children birth-weight ranged from 3 000 to 3 499 g, in 164 children from 3 500 to 3 999 g, and in 52 children from 4 000 to 4 499 g. One child weighed at birth 5 000 g. All the children were fully satisfactorily developed at the ages when the determinations were made. In no instance was the body-weight below that indicated by VON SYDOW as corresponding to the respective birth-weight. The number of determinations as to the quantities of breast-milk consumed, was 950 in male infants and 718 in female infants. Thus, a total of 1 668 primary data was obtained.

During the infant's second week of life breast-milk consumption (Table 1) amounted on the average from 487 to 489 g per day. It increased constantly, in the beginning rapidly, until at the age of three months, the amounts of breast-milk consumed ranged from 733 to 798 g. From then on the increase was much less rapid, and at the age of 4 months the highest mean value was equivalent to 747 g in girls, and to 821 g in boys. Subsequently, the intake seemed to remain on the same level. At the age of 6 months there even appeared to be a decrease. During the first two months the milk consumption of the girls corresponded, generally speaking, to that of the boys. Subsequently, the intake in girls was on the average by 75 g less than in boys (Fig. 1).

The study of the milk consumed within one and the same group of age is interesting. These variations are shown in Fig. 2 and in Table 1. The data contained in the Table were statistically analysed on the basis of the results obtained from the reported investigations. The variance within each group of age was greater than between the groups of age lying next to each other. The highest value within the group comprising the youngest children, was of greater magnitude than the lowest within the group to which the oldest children belonged. Thus, a child aged two weeks may consume more than 600 g per day and appears to require this quantity, whereas another child though aged six months may also develop satisfactorily if fed on the same quantity of breast-



Table 1.  
Female infants.

Age-groups	Body-weight					Amount of breast-milk consumed			
	Number of observations	Mean value	Normal variations	Variance		Mean value	Normal variations	Variance	
				Absolute	%			Absolute	%
2 w.	36	3 838	4 898—2 778	539	13.8	487	637—337	74.9	15.4
3 »	50	3 952	4 948—2 956	498	12.6	533	733—333	99.6	18.7
4 »	65	4 081	4 787—3 375	353	8.7	576	736—416	80.4	13.9
6 »	60	4 529	5 419—3 639	445	9.8	657	817—497	80.0	12.2
2 m.	70	4 834	5 854—3 814	510	10.6	704	900—508	98.2	13.9
3 »	43	5 591	6 685—4 497	547	9.8	733	969—497	118	16.1
4 »	46	6 323	7 689—4 957	683	10.8	747	1 023—571	138	18.5
6 »	26	7 563	9 005—6 121	721	9.5	740	970—510	115	15.6

Male infants.

Age-groups	Body-weight					Amount of breast-milk consumed			
	Number of observations	Mean value	Normal variations	Variance		Mean value	Normal variations	Variance	
				Absolute	%			Absolute	%
2 w.	50	3 977	4 883—3 071	453	11.4	489	611—367	60.8	12.5
3 »	47	4 166	4 979—3 351	407	9.8	571	781—361	105	18.4
4 »	58	4 351	5 149—3 553	399	9.2	645	839—451	97	15.1
6 »	69	4 743	5 699—3 787	478	10.1	685	991—479	103	15.0
2 m.	72	5 085	6 081—4 089	498	9.8	750	964—536	107	14.3
3 »	49	5 928	7 072—4 787	572	9.6	798	1 029—572	113	14.2
4 »	42	6 718	7 994—5 442	638	9.5	821	1 065—577	122	14.8
6 »	33	8 016	9 818—6 214	901	11.2	817	1 123—511	153	18.8



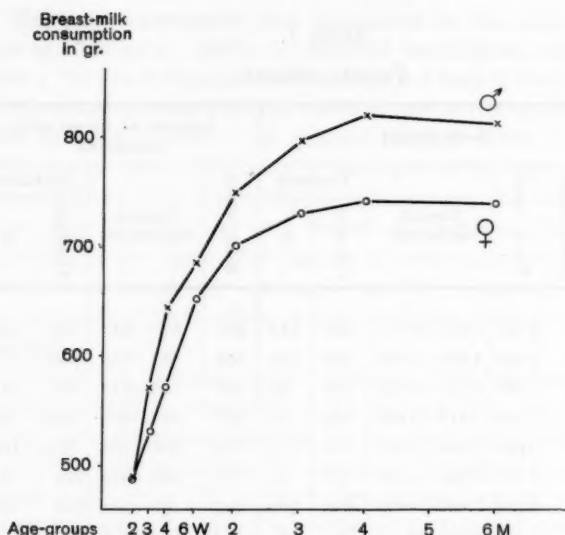


Fig. 1. Average breast-milk-consumption in gr. of male and female infants in different age-groups.

milk without showing any symptoms of requiring a larger amount of food.

Since the average intake of breast-milk increased in proportion to age (Fig. 2), it might be assumed that children belonging to the same age-group and presenting higher body weight would consume greater quantities of milk. Generally speaking, this does not seem to be the case. The breast-milk consumption of each group of age was plotted on the curves in relation to the child's body-weight and in accordance with sex. The charts show that, as regards the group of younger children, there is no relation between the weight of the child and its intake of milk (Fig. 3). On the other hand, in the groups comprising the oldest children, there is a comparative trend to greater milk consumption in children presenting higher body-weight (Fig. 4). There does not, however, exist any noticeable and statistically significant correlation between body-weight and breast-milk consumption.

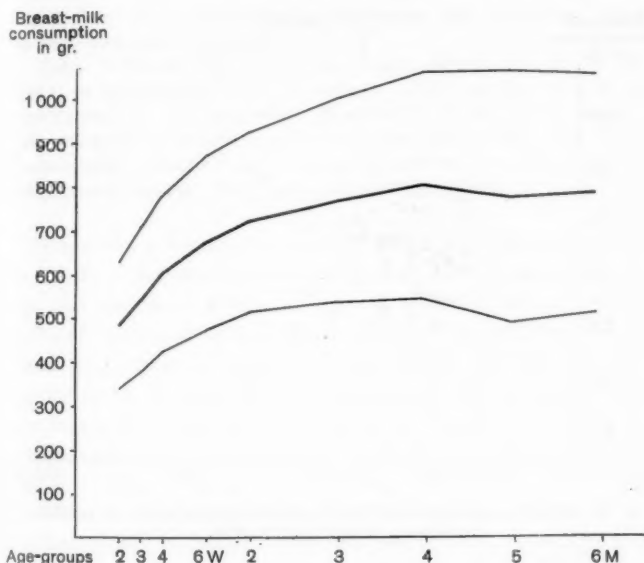


Fig. 2. The average amount of breast-milk-consumption in gr. and the upper and lower limit of its normal variations in different age-groups of infants.

The possible relation between weight and breast-milk intake was computed in the following manner. First, the weights were arranged in order of magnitude, and then each group of age was divided into four equally large parts. Fig. 3 and 4 shows the means. The statistical analysis<sup>1</sup> whether the means of the milk consumption within each part differed more from one another than was due to chance, was made by analysis of variance in accordance with SNEDECOR's F-test (SNEDECOR 1938, BONNIER and TEDIN 1940). The ratio between the variances is tabulated in accordance with the number of cases and groups included in the determination, and permits of an exact examination of probability (P) whether the groups coincide or differ. By this method the variation between the four means of milk consumption were compared with the variation within each part. From the results of the analysis it was deduced that the probability (P) of coincidence, generally, was 0.2 for the different groups of age. In some cases it

<sup>1</sup> At the statistical analysis a very valuable help has been delivered by Docent L. GOLDBERG for whose aimable co-operation the author will express his sincerest thanks.

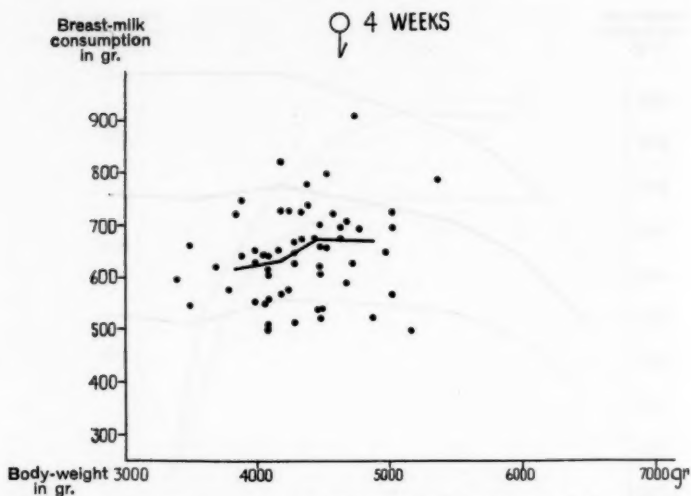


Fig. 3. Breast-milk-consumption of male infants aged 4 weeks in relation to variations of the body-weight.

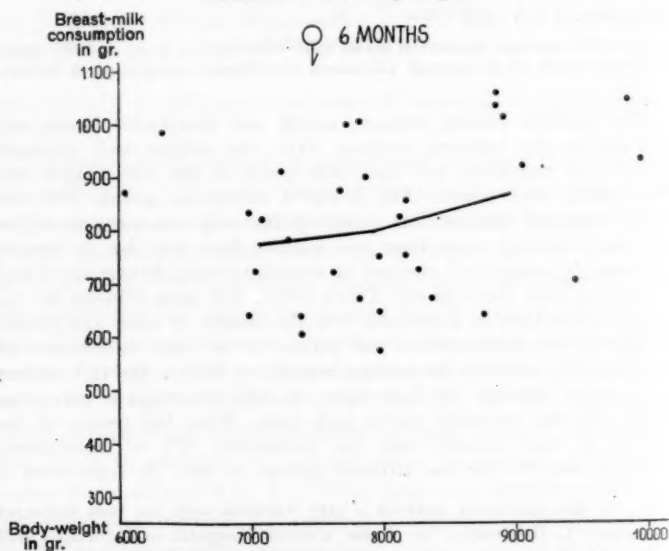


Fig. 4. Breast-milk-consumption of male infants aged 6 months in relation to variations of the body-weight.

ranged from 0.2 to 0.05, i. e. the difference fell within the limits of less than two times the standard error.

Table 1 further shows that the weight within each group of age varied, on the average by 10 per cent (8.7—13.8) of the mean, and milk consumption by 15.4 per cent (12.8—18.8). It results therefrom that milk consumptions varied in a higher degree than weight. Further, milk consumptions appears to be a comparatively constant percentage of the average consumption within each group of age (Table 1).

Since the present investigation demonstrated that there was no relation between body-weight and milk consumption within one and the same group of age, it must be assumed that the variance is caused by individual variances in different children. Thus, milk intake in a healthy child varied considerably. In two instances out of three the divergence from the average consumption in regard to age is equivalent to  $\pm 15$  per cent of the mean, and in nineteen out of twenty to  $\pm 30$  per cent of the mean, a fact that is demonstrated by the obtained values (Table 1).

When comparing two healthy and adequate children with one another, it will be found that in two cases out of three the variance is  $\pm 20$  per cent of the mean ( $15\sqrt{2}$ ), and in nineteen cases out of twenty it is equal to  $\pm 40$  per cent of the mean ( $30\sqrt{2}$ ).

The child's breast-milk consumption within each group of age is, no doubt, conditioned by other factors than by body weight. A child presenting elevated body size weight may consume smaller amounts of breast-milk than those consumed by a child of the same age of less body-weight. The child of a primipara is, as a rule, weighing less at birth than that of a multipara. Comparison of the breast-milk consumption of a child of a primipara with that of a child of a multipara yields results which are in good agreement with the fact that children presenting high body-weight, generally, do not consume larger quantities of breast-milk than children with small body weight. There is no definite difference between these two groups of children (Fig. 5). Likewise, no evidence was furnished that the age of the mother plays any significant rôle in the consumption of milk. If the average amount of consumed breast-milk at the different age-groups of children of average body-weight and the mother's age are taken

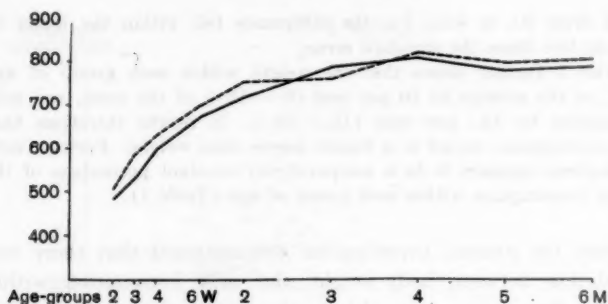


Fig. 5. Average breast-milk-consumption in gr. in different age-groups of first children (unbroken line) and of other (2d, 3d, etc.) children (broken line).

into consideration, no significant differences were found in the amounts of breast-milk relative to the age of the mothers (this calculation was performed by a matematicien, fil. kand. LARS LINDER).

The question whether the quantity of breast-milk intake in the infant corresponds to its actual requirement may give rise to arguments. Naturally, consumption and requirement need not be considered in all instances as identical. In the cases reported in this paper, the children were allowed to suck until they appeared to be satisfied, or had fallen asleep or relinquished their hold on the nipple. They were, on all occasions, allowed to consume as large a quantity of milk as they themselves desired and on which they seemed to thrive. This did not only apply to the test-days, but was the routine method at this Centre. Naturally, it cannot be definitely stated that a child that consumed a larger amount of milk than another child of the same age, actually required more food. If the child does not present any striking adiposity one is led to believe that the increased consumption is due to the fact that the child in question actually requires larger quantities of food. On the other hand, if the child's weight exceeds the average body-weight, one is easily led to consider the large quantity of milk consumed as »luxus consumption». On the other hand, this assumption does not hold good in all instances. If the child's weight, though being elevated, ranges within the limits of normal

Table 2.

Age-groups	Number of observations	Mean value of gr. milk per kg. body-weight	Mean value of cal./kg. body-weight	Variances
2 weeks	178	127.0	$88.9 \pm 1.3$	16.7
3 »	246	137.1	$96.0 \pm 1.1$	16.4
4 »	304	143.9	$100.7 \pm 0.9$	15.8
6 »	304	147.8	$103.1 \pm 0.9$	15.6
2 months	294	147.5	$103.8 \pm 0.9$	15.6
3 »	214	134.6	$94.2 \pm 1.0$	14.0
4 »	198	124.6	$87.2 \pm 1.0$	14.6
5 »	190	110.7	$77.6 \pm 1.1$	14.8
6 »	180	102.8	$72.0 \pm 1.0$	13.6

variation, the child should not be considered as overfed, and it is not justifiable to speak of luxus consumption. Since it was found that even in children of the same age the quantities of breast-milk consumed may vary to such an extent that variation from child to child may be equal to 100 per cent, the consumption of large quantities of milk should be considered as overfeeding only on condition that the child manifests obvious symptoms of overfeeding. The present material does not include any overfed children.

If the ration of a heavy eater was experimentally curtailed in such a manner that its milk intake corresponded to the mean value of the respective group of age, the child as a rule, responded with symptoms of discontent and seemed to suffer from hunger. Apparently, the child had adapted itself to the respective volume of consumption, and its requirements seemed to correspond to the quantity of milk the child had got used to and to which it responded satisfactorily. It may, therefore be said, that in normal, satisfactorily developed, breast-fed children consumption and requirement are identical.

It is of a certain interest to determine the caloric requirements of breast-fed infants by means of the values of milk consumption and its relation to body-weight as quoted above. The figures re-

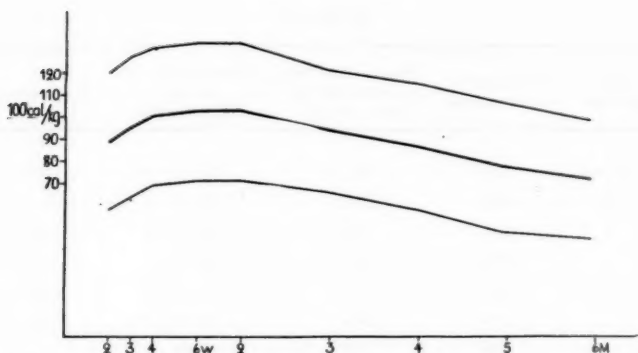


Fig. 6. Average caloric intake per kg. body-weight at different age-periods and its normal variations.

sulting from such a calculation, when the caloric value of breast-milk is assumed to correspond to 700 calories per 1 000 cc is seen in Table 2. Male and female infants are not separately considered in this investigation. The mean value is below 100 cal./kg body-weight during the 2d and 3d week, increases to 100 cal. or slightly more during the 4th to the 8th week, then decreases continuously and attains the value of 72 cal./kg body-weight at 6 months of age. During the 1st quarter of the 1st year of life the caloric requirement per kg body-weight is 97.7 and during the 2d quarter 78.9, and is thus a little below the usually accepted figures for these age-periods. The normal range of variation is seen in Fig. 6. Between the upper and the lower curve-lines lies 95 per cent of the observations.

## **Zur Kenntnis der Form des angulopyloralen Querfortsatzes (Querstücks) des kindlichen Magens und dessen Ringmuskulatur.**

Von

**WILH. WERNSTEDT.**

In einem Aufsatz in Acta pæd. Vol. XXXI, 1943, Seite 73 habe ich eine Übersicht über die Anatomie und die Motorik des angulopyloralen Querfortsatzes (Querstücks) des Säuglingsmagens gegeben. Aus dieser Darstellung geht hervor, dass das angulopylorale Querstück (»Antrum«, »Canalis») morphologisch in zwei von einander mehr weniger deutlich gesonderte Teile zerfällt (siehe Fig. 1), ein jeder mit einer nach aller Wahrscheinlichkeit teilweise verschiedenartigen Bewegungsart. Der kleinere neben dem Pylorus liegende Teil, das *Pylorusmundstück*, ist an der grossen Krümmung durch den Sulcus intermedius und an der kleinen Krümmung, manchmal weniger deutlich, vom grösseren Querstückteil, dem *Magenmotor*, abgesetzt. Der Magenmotor streckt sich an der kleinen Krümmung oral bis zur Incisura angularis. An der grossen Krümmung findet man keine am Umriss hervortretende Abgrenzung. Die Grenze ist aber zu dem Punkt zu verlegen, wo die durch die Incisura angularis einsetzende Ringwelle die grosse Krümmung schneidet. Dieser Punkt kann annähernd bestimmt werden, wenn man der an der Incisur gelegenen Muskelschlinge (»Sphincter angularis«) folgt, die denjenigen Muskelschlingen am nächsten liegt, die von der Incisur über die Pars angularis radiieren. Der Schneidepunkt liegt, wie auch am Röntgenschirm zu sehen ist, gewöhnlich ein wenig pyloral von der am meisten kaudal liegenden Rundung der Pars angularis.



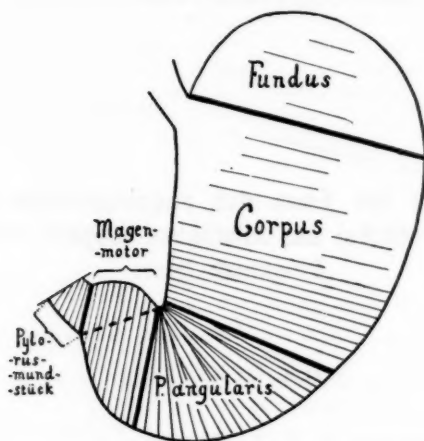


Fig. 1. Schematische Darstellung des Magens und seiner Teile.

Die *Querstückperistaltik* verläuft im allgemeinen nicht einheitlich. Die *Motorperistaltik* besteht, wie es scheint, ausschließlich von Ringwellenbewegungen. Die am meisten charakteristische *Mundstückperistaltik* ist aber die s. g. »Schlusskontraktion«. Diese konzentrische Zusammenziehung führt bei der spastischen Pyloruskontraktur (beim Pylorospasmus) der Säuglinge zu der charakteristischen *Mundstückkontraktur*, die die pathologisch anatomische Unterlage dieser Krankheit ist.

Es wird meine Aufgabe sein hier eine eingehendere Beschreibung des angulopyloralen Querstücks des kindlichen Magens zu geben wie sie aus einer Untersuchung von 50 Mägen hervorgeht (siehe die Tabelle). Sämtliche Organe sind ad maximum mit Luft ausgespannt und dadurch in ihre Grundform übergeführt worden. In diesem Zustand wurden die allermeisten nachher getrocknet. Einige Mägen sind nach der Dilatierung entweder ungehärtet oder nach Härtung in Formalin disseziert worden. Vor dem Aufblasen wurden die als Incisura angularis und Sulcus intermedius hervortretenden postmortalen Einkerbungen der Magenwand mit Tinte markiert. Die meisten Organe gehören dem Säuglingsalter.

Tabelle.

Die Längenmasse sind in Millimeter, die Lage der Incisur und des Sulcus intermedius in Verhältnis zu den postmortal als Incisur und Sulcus hervortretenden Einkerbungen angegeben. Die debilen in der ersten Wochen gestorbenen Kinder (unter 2500 Gm) sind nicht bezüglich Alters sondern Gewichts angeführt.

Nr.	Alter			Incisur			Länge			Lage					
				bogen- för- mig	Winkel		Mundstück		Quer- stück	Incisur			Sulcus		
	J.	M.	T.		stumpf	recht	spitz	Curv. min.		Curv. maj.	gleich	oral	pyloral	gleich	oral
27		1360			+			8	12				+	+	
46		1380					+	7,5	10,5	+					+
14		1420				+		3	7	10					
10		1570				+		1	7	17					
5		1600			+			3	7	14					
20		1720		+					6,5				+		+
21		1970				+			12,5		+			+	
48		2210				+			11	15					
15			0		+				9	10	+				+
39			2				+	3	13	16,5	+				+
11			4			+		3	12	13		+		+	
4			5			+			14						
18			9			+			9,5	10				+	
23			11				+		8	13	+				
37			20			+		1	10	14	+			+	
35			24		+				11	14					+
16			25			+		5	10	16		+		+	
2		1					+								
42		1	7				+		11,5	16	+				
50		1	11				+		12	17		+		+	
9		1	14			+		5	13	18	+				+
33		1	14			+			12,5	15			+		
8		1	15			+		2,5	14	17	+				+
6		1	19		+			3	10	14		+		+	
28		1	22				+		8,5	23	+				+
13		1	25			+			10,5	15		+			

Nr.	Alter			Incisur			Länge			Lage						
				bogen- förmig	Winkel		Mundstück		Quer- stück	Incisur			Sulcus			
	J.	M.	T.		stumpf	recht	spitz	Curv. min.		Curv. maj.	gleich	oral	pyloral	gleich	oral	pyloral
22		2	24			+			12	16	+			+		
26		2	27					+		19	+			+		
41		3	28				+		2,5	9	15,5	+				
36		4	15					+		14,5	23,5	+				+
47		7	25				+			13	21		+			+
43		7	26	+					3,5	17	23		+			
25		7	26		+				1,5	15,5	16,5		+		+	
7		9	1		+					10	18	+			+	
49		10	6			+				12,5	18	+			+	
3		10	24				+		3	18	32		+		+	
29		11	23				+			15	24		+			+
30	1		6					+	1	13	23			+	+	
1	1	1	5							10						
32	1	2	21		+					17	21	+			+	
44	1	7	4			+				17	32	+			+	
38	1	8	15		+				4,5	16	29			+	+	
34	1	11	27				+			12	29		+		+	
31	3	6	4		+				7,5	19,5	27					
40	3	9	2				+			21	31			+		+
17	4	1	27		+					17	25					
24	6		8			+				22	30	+			+	
12	7	2	13				+		3	19	30	+				+
19	7	10	27				+			20	30	+			+	
45	13	4	2				+			25	32	+			+	

An dem in seine Grundform übergeführten Magen findet man die *Curvatura minor* etwa an der Grenze ihrer mittleren und kaudalen Drittel beinahe ausnahmslos eine kräftige, manchmal ganz unvermittelte öfter abgerundete, winkelförmige Umbiegung (*Incisura angularis*) machen. In 19 Fällen war die Incisur recht-, in 16 Fällen spitz-, in 11 Fällen stumpfwinkelig. In 3 Fällen

trat die Incisur mehr als eine allmählich bogenförmige wie als eine winkelige Umbiegung hervor. Die recht- oder spitzwinkelige Umbiegung war folglich die gewöhnlichste Form. Die stumpfwinkelige Biegung war seltener und die bogenförmige Umbiegung gehörte mehr zu den Ausnahmen (Fig. 2—6 und 10—13). Eine zwischen den beiden hervortretendsten Ausbuchtungen der grossen Kurvatur Fundus und Pars angularis (Fornix bzw. Sinus), gezogene Linie bildet aber mit einer durch die Mitte des Querstücks gezogenen Linie (Querstückachse) in den allermeisten Fällen einen spitzen Winkel (siehe die Figuren).

Ventro-dorsal gesehen zeigt das angulopylorale Querstück Trichterform, wobei der orale Umfang wesentlich weiter ist als der pylorale. Gewöhnlich wird der Magen nur ventro-dorsal gesehen. Er und besonders sein Querstück verdient doch von Kurvatur zu Kurvatur betrachtet zu werden. In dieser Projektion zeichnet sich das Querstück noch schöner in Trichterform ab (Fig. 7—9). Der ventro-dorsale Durchmesser an der Grenze der Pars angularis ist 2 bis 3—3½ mal so gross als der Pylorusdurchmesser, derjenige von Kurvatur zu Kurvatur manchmal noch grösser. Nur in gewissen Funktions-(Kontraktions-)lagen kann dieser Teil wie jeder beliebige Teil des Magens Zylinder-(Kanal-)form annehmen. Tatsächlich findet man auch postmortal diesen Teil öfter als andere Teile des Magens röhrenförmig zusammengezogen. Dies ist in Betracht der im Querstück stattfindenden kräftigen Motorik kaum überraschend. Beachtung verdient, dass man weder in den Säuglingsmägen noch in denen der älteren Kinder irgend eine Andeutung der von RETZIUS bei Erwachsenen beschriebenen blasenförmigen Ausbuchtung des dem Pylorus am nächsten gelegenen Teil der kleinen Kurvatur findet.

Die Pylorusöffnung ist bald kreisförmig, bald oval und dann mit dem längsten Durchmesser in verschiedenen Richtungen in verschiedenen Fällen.

Manchmal wölbt sich die dem Magenmotor gehörige Membrana angularis unmittelbar am Pylorusmundstück ampullenförmig hervor. Unter diesen Umständen setzt sich das Mundstück an die Minorseite scharf vom Magenmotor ab (Fig. 3, 4 u. 6). Gewöhnlicher ist aber, dass die Grenze des Mundstücks deutlicher an

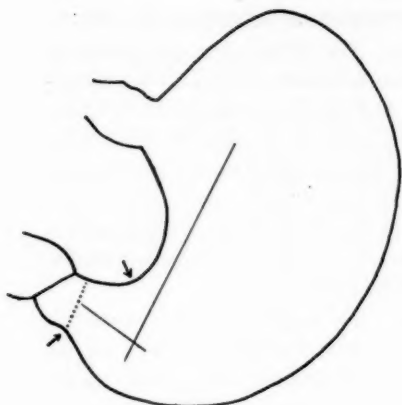


Fig. 2.



Fig. 3.

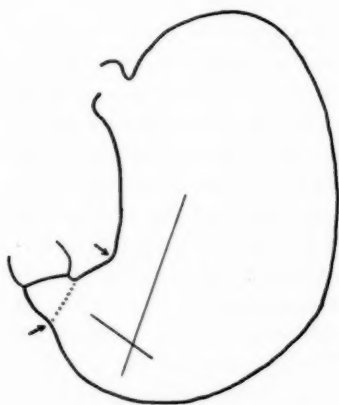


Fig. 4.

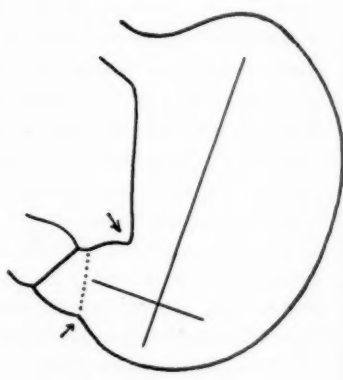


Fig. 5.

der grossen als an der kleinen Kurvatur hervortritt. Fast ausnahmslos trennt ein wenigstens andeutungsweise vorkommender *Suleus intermedius* hier die beiden Querstück- (»Antrum-«, »Canalis-«) teile von einander ab. Sind die Grenzen des Mundstücks sowohl an der kleinen als an der grossen Kurvatur besonders scharf, tritt es ebenso deutlich hervor wie an den (dilatierten)

Fig. 2—5. 2 (Nr. 35) bogenförmige, 3 (Nr. 38) bogenförmig-stumpfwinkelige, 4 (Nr. 6) stumpfwinkelige, 5 (Nr. 18) rechtwinkelige, und 6 (Nr. 12) spitzwinkelige Incisur. Fig. 3, 4 und 6 mit an beiden Kurvaturen scharf abgegrenztem Pylorusmundstück.

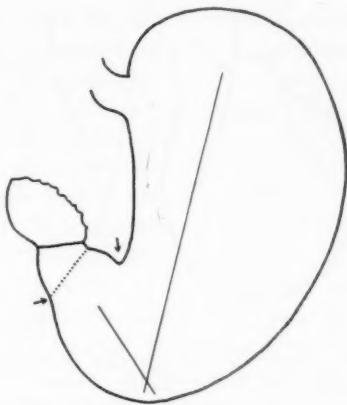


Fig. 6.

Mägen der spastischen Pyloruskontrakturen im Säuglingsalter. Das heisst es ähnelt einer aus einem bogenförmig gebeugten Rohre ausgeschnittenen kleinen keil- oder zirkelsektorförmigen Ringpartie (Fig. 3, 4 u. 6). In 18 Fällen = 36 % des ganzen Materials und in 14 Fällen = 37,8 % der Säuglingsmägen war dies der Fall. Unter den von mir 1906 publizierten Mägen blieb nach den Ausdehnungsversuchen im ganzen Material in 11 (23 %) und unter den Säuglingsmägen in 9 (22 %) der Fällen eine mundstückähnliche (»stenoseähnliche«) unvollständig dilatierte Partie zurück, die offenbar mit dem Pylorusmundstück identisch war.

Der auffallende Unterschied in der Häufigkeit des Hervortretens dieser »stenoseähnlichen« Partie in den beiden Serien ist wahrscheinlich darauf hinzuführen, dass ich 1906 die Vorderungen strenger stellte als heute. Damals, da sich das Hauptinteresse an die so in die Augen fallende charakteristische Form der Mundstückkontraktur der dilatierten pylorospastischen Mägen besonders knüpfte, habe ich wahrscheinlich zu den »stenoseähnlichen« Mägen nur diejenigen Organe gerechnet, wo das Mundstück sich ebenso scharf gegen den Magenmotor absetzte als bei den in ihre Grundform übergeführten pylorostenotischen Mägen. Vielleicht haben auch die verschiedenen Behandlungsmethoden der beiden Serien



Fig. 7.



Fig. 8.

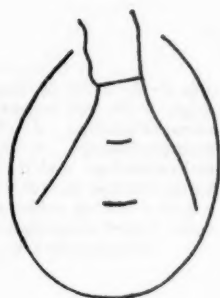


Fig. 9.

Fig. 7—9. Die von Kurvatur zu Kurvatur gesehenen trichterförmigen Querstücke der Mägen Nr. 27, 17 und 18. Die horizontalen Linien bezeichnen die Grenze des Pylorusmundstücks bzw. des Magenmotors.

(Wasserausspannung — Fomalinhardtung einerseits und Luftaufblasen — Trocknen andererseits) dazu mitwirken können.

Das Mundstück misst an der kleinen bzw. an der grossen Kurvatur der Mägen von 10 *ausgetragenen* Säuglingen 1—5 bzw. 8—18 Mm. Dies ist beinahe dieselben Masse (1—5 bis 6 bzw. 9—18 Mm) wie an den 5 gemessenen »stenoseähnlichen« Säuglingsmägen des Materials von 1906. Die Mundstückkontraktur der 1906 publizierten Pylorospasmmägen erreichte in 7 einwendungsfreien Fällen 2—9 bzw. 15—21 Mm. *Das kontrakturierte Mundstück der pylorostenotischen Mägen ist folglich, wie man schon a priori auf Grund der starken Kontraktion und Hypertrophie erwarten konnte, grösser als das Mundstück der normalen Organe.*

Ich habe aus dieser Zusammenstellung der kontrakturierten Mägen von 1906 ausser den unsicheren (umgeklammerten) Masse noch einen Magen mit den angegebenen Massen 18 bzw. 26 Mm ausgeschlossen. Wie aus der Reproduktion hervorgeht (siehe Fall II Nord. Med. Ark., Abt. II, 1906) gibt es in der Tat hier keine unzweideutige Grenze des Mundstücks an der kleinen Kurvatur. Das angegebene Mass 18 Mm, das so stark von allen anderen entsprechenden Massen abweicht, kann kaum als dem Mundstück ausschliesslich gehörend angesehen werden.

Der ganze Querfortsatz variiert in der Länge (Incisura angularis—Pylorus) in den hier untersuchten Säuglingsmägen zwischen 10—32 Mm. In meinem Materiale von 1906 sind die entsprechenden Masse 9—23 Mm. Da nur ein einziger Magen in der neuen Serie 24 Mm übersteigt, ist folglich in dieser Hinsicht die Übereinstimmung zwischen der alten und der neuen Serie ziemlich gut. Die Querstücklänge misst in den 13 Mägen älterer (1—13jähriger) Kinder 21—32 Mm. Die entsprechenden Masse der 7 Mägen der 1—14jährigen Kinder von 1906 waren 17—37 Mm.

Nach der Ausspannung fand man (im ganzen Material) die fixe, in der Grundform hervortretende Incisur in 22 Fällen mit der postmortalen Incisur zusammenfallend. In 11 Fällen lag sie oral und in 6 Fällen pyloral von dem postmortal als Incisur mit Tinte markierten Punkt. Sulcus intermedius verus fiel in 21 Fällen mit dem postmortalen Sulcus zusammen, in nur einem Falle befand er sich oral, in 13 Fällen pyloral von der Markierung. In etwa der Hälfte der Fälle fiel demnach die fixe Incisur und der fixe Sulcus mit den postmortal als solche hervortretenden Einkerbungen zusammen. Wo sie anders lagen, war der Sulcus verus fast ausnahmslos mehr pyloral gelegen als der Pseudosulcus. Die Incisur dagegen befand sich öfter oral (11 mal) als pyloral (6 mal) von der postmortal gefundenen.

Über den Verlauf der Ringmuskelschlingen des Querstücks kann man sich sowohl am frischen als am getrockneten Organ durch Betrachtung (ev. mit Hilfe des Vergrößerungsglases) in wechselnder Beleuchtung orientieren. Im getrockneten Präparat sieht man gewöhnlich eine feine Querrunzligkeit an der Oberfläche, wodurch die Untersuchung des Verlaufes der Ringmuskelschlingen erleichtert wird. Am leichtesten ist es dem Verlauf derselben an den Mägen debiler Säuglinge zu folgen. Je älter die Kinder werden um so kräftiger sind die Ligamenta ventriculi entwickelt und durch diese wird der Verlauf der zirkulären Muskelbündel unterbrochen. Besondere Schwierigkeiten bietet es dann manchmal den Muskelbündeln über dem Mundstück zu folgen, insbesondere weil auch die den ganzen Mundstück herumziehende längslaufende Muskulatur mit den Jahren an Masse zunimmt. Am Magenmotor und ganz besonders über dessen kranialem





Fig. 10.

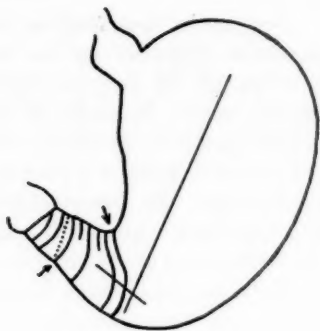


Fig. 11.

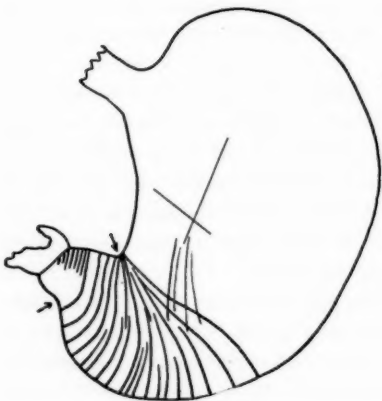


Fig. 12.

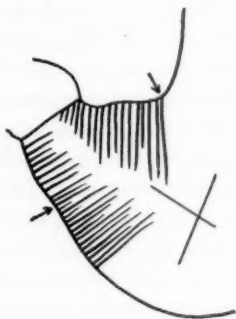


Fig. 13.

*Fig. 10–12.* Anordnung der Ringmuskelbündel im Querstück der Mägen Nr. 13, 23 und 27. *Fig. 13* (Nr. 17) mit eingezeichnete schematisierte Anordnung der Ringmuskelbündel des Querstücks. *Fig. 10 und 13* mit stumpf-, *Fig. 11* mit spitz- und *Fig. 12* mit rechtwinkliger Incisur.

Umfang (der Membrana angularis) lässt sich der Verlauf der zirkulären Muskelschlingen indessen immer ohne Schwierigkeit folgen.

Charakteristisch ist, dass die Muskelbündel immer einen Verlauf von rechts kranial nach links kaudal nehmen. Die Muskelschlingen laufen also in einer Ebene, die schräg (oder quer) die Ebene Incisura angularis—Sulcus intermedius wie auch die



Fig. 14.

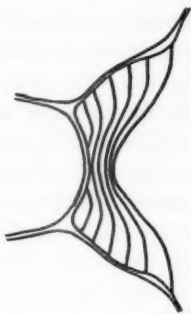


Fig. 15.



Fig. 16.

*Fig. 14—16.* Schematisierte Zeichnung der von innen freigelegten Ringmuskulatur des Pylorusmundstücks. *Fig. 14* an der kleinen, *Fig. 15* an der grossen und *Fig. 16* an beiden Kurvaturen aufgeschnittener Mägen.

Pylorusebene schneidet. Dagegen nehmen sie einen mit der oralen Abgrenzung des Mundstücks mehr parallelen Verlauf. In den Mägen der kleinsten Kinder findet man gewöhnlich, dass die Muskelschlingen besonders kaudal von den noch schwach entwickelten Ligamenten sich bogenförmig nach rechts etwas biegen, so dass sie tatsächlich schiefe mit der Konkavität gegen den Pylorus gerichtete Ringen bilden. Bisweilen zeigen die Muskelbündel in ihrem Verlauf von Kurvatur zu Kurvatur sogar Andeutung einer S-förmigen Biegung (Fig. 10—12).

Wo die Muskelschlingen durch entwickelte Ligamenta ventriculi fixiert werden, stellen sich die kranialen und kaudalen Bogen derselben im ganzen Querstück mehr weniger stumpfwinkelig gegen einander. Sie nehmen etwa denselben nach dem Pylorus gerichteten Verlauf wie die Stacheln der Wirbelsäule der Fische oder wie die einzelnen Fahnen auf beiden Seiten des Federstiels (Fig. 13). Die dem Pylorus am nächsten liegenden Muskelbündel werden in ihren kranialen Bogen durch den Pylorus unterbrochen und tauchen in die Pylorusmuskulatur hinein. Die kaudalen Teile der Muskelbündel nehmen dagegen etwa dieselbe Richtung ein wie der schräggestellte Pylorus.

Wenn man einen aufgeblasenen Magen der grossen Kurvatur entlang aufschneidet, sieht man nach der Entfernung der Mucosa,

wie die zirkulären Muskelbündel von den beiden muskeldicken Minorschnittflächen des Mundstücks in immer weiteren Bogen den ausgebreiteten Pylorus umgeben (Fig. 14). Schneidet man aber die grosse Kurvatur auf, findet man unter der entfernten Schleimhaut wie die Muskelbündel vom kurzen Minorteil des Mundstücks und dem nächstliegenden Pylorusteil gegen die aufgeschnittenen Ränder der grossen Kurvatur ausstrahlen (Fig. 15). In dem an beiden Kurvaturen aufgeschnittenen Mundstück beobachtet man schliesslich (Fig. 16), wie die von innen freigelegten Muskelbündel mit ihren nächst dem Pylorus liegenden kranialen Teilen in den Pylorus eintauchen, gerade wie man es schon von aussen sehen kann. *Das ganze Pylorumundstück bildet mit dem Sphincter Pylori und dem Sphincter intermedius, welche beiden Sphincter das Mundstück beiderseits umfassen, und sich auch — wenn der Minorteil des Mundstücks nicht ungewöhnlich lang ist — mit einander kranial zusammenweben, ein Schliessmuskelsystem, das sich bei der »Schlusskontraktion« und beim Pylorospasmus fest kontrahiert.*

Die Resultate lassen sich folgendermassen zusammenfassen:

1) Der angulopylorale Querfortsatz (Querstück) des kindlichen Magens hat Trichterform, die sich beim Betrachten des Magens von Kurvatur zu Kurvatur besonders schön abzeichnet. Das Querstück biegt sich gewöhnlich recht- oder spitzwinkelig, weniger oft stumpfwinkelig oder in regelmässiger Bogenform vom übrigen Magen nach rechts ab.

2) Die Bündel der Ringmuskulatur des Querstücks bilden gegen den Pylorus konkav gebogene Muskelschlingen. Wenn die Ventrikelligamente ausgebildet sind, teilen sie die Ringbündel in einem kranialen und einem kaudalen Teil. Die kranialen Teile der Schlingen schneiden schräg die Pylorusebene und die Ebene Incisura angularis—Suleus intermedius. Die kaudalen Bogenteile verlaufen den genannten Ebenen mehr weniger parallel.

3) Die Länge des Querstücks mass an den Säuglingsmägen 10—32, an den Mägen älteren Kinder 21—32 Mm.

4) Das typische Aussehen des Pylorusmundstücks als ein kleines keil- oder zirkelsektorförmiges Ringstück trat in 36 % der Fälle deutlich hervor.

5) Die Länge des Mundstücks des Säuglingsmagens ausge-tragener Kinder mass an der kleinen Kurvatur 1—5, an der grossen Kurvatur 8—18 Mm. Der Mundstückkontraktur der pylorospastischen Säuglingsmägen von 1906 erreichte 2—9 bezw. 15—21 Mm.

6) Der kraniale Teil der dem Pylorus am nächsten liegenden Ringbündel tauchen in den Pylorusvalvel hinein. Die ganze Ring-muskulatur des Mundstücks mit dem Pylorussphincter und dem mit ihm auch gewöhnlich kranial verflochtenen oder dicht neben ihm liegenden Sphincter intermedius bildet ein pylorales Schliess-muskelsystem, das sich bei der »Schlusskontraktion« und dem Pylorospasmus der Säuglinge kräftig zusammenzieht.

7) Die Incisura angularis und der Sulcus intermedius fielen in etwa der Hälfte der Fälle mit den postmortal als Incisur und Sulcus imponierenden Einkerbungen zusammen. Wenn nicht damit zusammenfallend lag der Sulcus fast ausnahmslos mehr pyloral als der postmortale Pseudosulcus, die Incisur dagegen öfter oral als pyloral von der postmortalen Pseudoincisur.

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**Schrifttum.**

Betreffs der Literatur siehe das Verzeichnis meines Aufsatzes in *Acta paed.*, Vol. XXXI, 1943.

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## On Shock in Premature Children.

### Preliminary Report.

By

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As far as can be judged from the literature, very divided opinions still prevail as to the cause of death — at least certain of the numerous deaths — among the prematurely born. I refer in the first place to PEIPER's monograph, from which I have taken some introductory points of view on the subject. It may be said that the divergence in opinions is chiefly due to the fact that one school sees the main cause of death in the majority of cases in the prematurity, or rather the congenital weakness (debility), while the other school maintains that, in principle, death is always caused by more or less distinct anatomical lesions, chiefly within the nervous system and the respiratory organs. Thus YLPPÖ and, later, SCHWARTZ, maintained that in autopsies on the prematurely born, in the great majority of cases there are hemorrhages in the meninges or brain, and that these hemorrhages are a result of trauma caused by the delivery. The asphyctic condition, which in these cases most frequently immediately preceded death, is secondary to these hemorrhages. HORTINGER points out that in practically every case there are positive autopsy findings, as a rule in the nervous system in the form of hemorrhages, or in the lungs in the form of atelectasis or pneumonia, and that for that reason the conception of congenital weakness as the cause of death is unfounded and unnecessary.

PEIPER has, in my opinion correctly, polemized against this one-sided view. He points out, *inter alia*, that here, as in the case of certain other morbid conditions, a distinction must be made

between the basic illness and the immediate cause of death. PEIPER recalls the aspiration pneumonia usually occurring in carcinoma of the stomach, and the diabetic gangrene with the accompanying general sepsis. Just as, in indicating the cause of death, it is wrong to allow the aspiration pneumonia in the prematurely born to overshadow the fundamental illness, the debility (which favours the appearance of the aspiration), so it is wrong to allow the immediate — and to a certain extent, accidental — cause of death to overshadow these fundamental diseases. PEIPER further points out the importance of the clinical picture and of the clinical study in judging the cause of death. In most cases very immature foetuses which are removed by Caesarean section, without any trauma worth mentioning, inevitable die a few minutes after birth with the picture of asphyxia, without there being any reason to reckon with any definite anatomic lesion as the cause of death. But even if autopsy reveals an anatomic lesion, PEIPER says, this does not necessarily imply that this was the cause of death. YLPPÖ and SCHWARTZ are of the opinion that the asphyctic attacks in the debile are practically always due to traumatic hemorrhages in the medulla oblongata or its immediate surroundings, arising during delivery. Together with CREUTZFELDT, PEIPER made a thorough anatomic examination of the brains of 7 premature children who had exhibited respiratory disturbances of the central type, but was not able in any of the cases to prove hemorrhages in or in the neighbourhood of the medullary respiration centre. Thus, the cases of apnoea are not necessarily caused by provable lesions in the respiration centre. PEIPER also raised the justifiable objection to YLPPÖ's and SCHWARTZ's points of view, that it is not simply a matter of course that the causal connection between the hemorrhages proved at autopsies and the cessation of respiration is the one assumed by YLPPÖ and SCHWARTZ. PEIPER points out that the state of suffocation (asphyxia) can give rise to hemorrhages in practically all the internal organs, *inter alia*, the brain. In view of the great vascular fragility in the premature which has been proved, *inter alia*, by YLPPÖ and his co-workers, it is — according to PEIPER — not impossible that asphyxia in the premature may

give rise to greater hemorrhages than usual in deaths from suffocation in non-premature children or adults. BARTH produced asphyxia in pregnant guinea-pigs by means of suffocation with carbon dioxide. In these cases there were hemorrhages in the ventricles of the brains of the foetuses and, especially, considerable hemorrhages in the meninges, but on the other hand, not in the nerve substance itself. Thus PEIPER's view that at least some of the intracranial hemorrhages which are found in connection with death from asphyxia among the premature are secondary to the asphyxia, not its cause, finds experimental support.

PEIPER summarizes his discussion of the clinical pathology of the premature as follows: "Das Hauptleiden der Unreifen, die angeborene Lebensschwäche, besteht in der mangelhaften Tätigkeit lebenswichtiger Organe. Atemschwäche, Saugschwäche, Gefäßschwäche, Schwäche der Wärmeregulation und Resistenzschwäche gegenüber Infekten und Ernährungsstörungen, — — — gefährden das unreife Kind und können mittelbar oder unmittelbar den Tod herbeiführen. Eine Schwäche des Kreislaufs, der Ferment- und der Hormonbildung ist dagegen nicht mit Sicherheit nachzuweisen."

On the basis of clinical and pathological observations, I arrived several years ago at the conclusion that, in the debile, shock conditions and liability to shock must probably be taken into consideration as factors of importance in connection with the severe morbid conditions and deaths which are so frequently met with among these children.

Firstly, with regard to the clinical side of the matter, I would draw attention to the following circumstances, which will probably be well known to everyone who has had a good deal to do with the care of the premature in hospitals. Death in the premature, if it does not supervene very soon after birth, does not usually take place suddenly in the form of asphyxia coming like a bolt from the blue. As a rule death is preceded by a more or less prolonged state of a more or less affected general condition, pronounced pallor or ashen grey colour of the skin, occasionally with more or less pronounced cyanosis and extreme general weakness. This usually manifests itself in maximal absence of movement,

increased general flaccidity and reduced respiration movements; and, further, there is usually an increased requirement of warmth to maintain the temperature of the body. Loss of weight or absence of weight-increase are also typical symptoms, as are also greater difficulties in feeding. Sometimes hemorrhages appear. More or less frequent attacks of asphyxia often make their appearance, and death most frequently supervenes in association with such an attack. As far as I can find, this clinical picture is certainly not in any way pathognomonic of shock — as is well known there is no pathognomie, purely clinical shock picture — but it tallies well with what is typical in clinical shock. I shall return to this question later.

For some months I have myself performed, or have been present at, practically all the autopsies from the relatively large premature department at the Gothenburg Children's Hospital. I have been able to verify an observation which I had made earlier, namely the great blood congestion met with in certain internal organs, especially in the liver. In this preliminary paper I shall not present any more detailed casuistics. I will content myself with describing *the usual post-mortem finding in these cases, especially as regards the liver, which is almost always dark bluish-red in colour. Its cut surface exhibits a particularly great abundance of blood, so that large quantities of blood flow from the fresh section surface without pressure.* Both from my own observations and from discussions with the experienced pathologists at the Sahlgren Hospital, in whose pathological-anatomical institution these examinations were made, I have come to the definite conclusion that such an abundance of blood is seldom met with in the liver in other cases, and it is clearly characteristic of the premature. Even in cases of acute stasis of the liver such large amounts of blood do not as rule flow from the liver.

In microscopic control of the macroscopic finding one is struck by the great abundance of blood, and also by the often particularly wide intra-acinous capillaries. YLPPÖ has pointed to the fact that in the premature the liver is abundant in blood, both macroscopically and microscopically, but as far as I can find he has not attached any special importance to this finding or discussed its significance



or implications. In other internal organs, too, there is sometimes a somewhat conspicuous abundance of blood. Most frequently, but far from regularly, there is an increased blood content in the kidneys, generally in the pyramids or on the borderline between the pyramids and the cortex. However, I have never seen an abundant flow of blood from a section surface. The lungs also exhibit a great blood content at times, which appears most frequently and most pronouncedly in atelectatic lungs or parts of lungs with small air content. The mucous membranes of the stomach and intestines practically never exhibit any appreciable hyperaemia. Petechiae, such as are usually found in cases of death from suffocation, were common, but not constant, findings. Hemorrhages in the meninges were also relatively common. Only occasional cases of obvious traumatic hemorrhage, as a result of rupture of the tentorium, were met with.

From the clinical point of view, the cause of death in the majority of cases appeared to be a result of debility. In some cases, signs of infection, in the form of colds or coughs ushered in the lowered state which culminated in death. In most cases typical signs of infection as the initial stage of the poor or deteriorated condition were absent. Both clinically and anatomically, aspiration of food or the contents of the stomach occurred only in exceptional cases. In the casuistics on which these observations are based, abnormalities within the heart or the large vessels are not included.

*The first interpretation that suggests itself of the remarkably strongly pronounced abundance of blood in the liver is that it is an expression of a state of shock. The macroscopic and microscopic findings do not at all resemble those met with in stasis. Thus, no especial dilatation of the central veins was observed, nor any changes in the macroscopic markings of the cut surface of the liver of the type which are usual in stasis owing to heart failure.*

In cases of shock, visceral hyperaemias are usual and typical. It is in the first place MOON (to whose well-known shock monograph I refer, both here and below) who has occupied himself more in detail with the anatomical findings in clinical and ex-

perimental shock. He points out that visceral hyperaemia, both macroscopic and microscopic, is the most characteristic feature in cases of shock. This hyperaemia is usually most marked in the lungs, the liver and the kidneys, but it is also pronounced in the central nervous system, on the serous surfaces, in the mucous membranes of the stomach and intestines, as also in other visceral organs, such as the pancreas and suprarenal glands. If this typical anatomical picture of shock described by MOON and others is compared with the anatomical finding in the premature, it is clear that in the majority of cases the visceral hyperaemia in the premature is especially pronounced only in the liver. For this reason it may perhaps be questioned whether the findings discussed here are typical of shock. In his monograph, MOON points out that it is not infrequently found that the hyperaemia is more pronounced in one organ system than in another. Since I began to interest myself in the possible anatomical shock findings in the premature, I have had an opportunity of seeing some autopsies, which — judging from the clinical and anatomical diagnoses — revealed shock. Thus quite recently I attended the autopsy on a little child that had died of perforation peritonitis after a neglected invagination. The lungs exhibited slight hyperaemia, as did the liver. The intestinal mucous membrane was not — macroscopically at least — abnormally abundant in blood. The liver hyperaemia was not nearly as great as in the premature.

The great abundance of blood and the strong capillary dilatation in the liver in the premature without the signs typical of cardiac stasis — in cases of pronounced shock there is always capillary stasis — are, as far as I can find, of the same nature as the more or less pronounced hyperaemia present in cases of typical shock. (MOON.)

I have also examined the condition of the liver in some stillborn foetuses, both full-term and immature. On the whole the liver exhibited the same picture as in the premature. Intra-uterine fetal death or the death of the fetus during parturition will, in principle, always be death from asphyxia, whether it is caused by direct suffocation, as will usually be the case, or is due to

cessation of the action of the heart. Thus death from asphyxia in the new-born appears to be regularly associated with an excess of blood in the liver of the type usual in shock. And this brings me to the question of the connection between asphyxia and shock. MOON and others working on shock research emphasize the intimate connection between the two. Asphyxia gives rise to shock, owing to damage to capillaries and to parenchyma cells, and shock, or rather the disturbance in capillary function, which is the significant feature of every state of shock, gives rise to asphyxia in the parenchyma cells of the organs affected. In both cases it is a question of anoxemia, general or local. Anoxemia plays a great part in the vicious circle mechanism which always cooperates in a progressive state of shock.

Hemorrhages, both capillary and venous, are usual in shock, as they are also usual in asphyxia and in the premature. Thus, here too, there is close agreement between the ordinary picture of shock and the autopsy finding in the premature and asphyctic new-born.

Many circumstances indicate that an important side of the nature of debility is a defective development of the capillary network and an imperfect capillary function. Thus MALI and RÄIHÄ considered that they found that the capillary network of the premature, specifically in the brain and liver, is wider-meshed the more immature the child is. If these investigations are confirmed, this implies that the supply of oxygen for the parenchyma cells in these organs is the poorer the greater the immaturity. The risk of anoxemia, and thus of shock, thereby becomes increasingly great. The same authors also found the greater capillary fragility with the injection of dye solutions the more pronounced the immaturity was. YLPPÖ has found that the powers of resistance to under-pressure in the capillaries is lower in the premature than in the immature. YLPPÖ's statement that the degree of this reduction bears a relation to the birth weight, and thus is in close relation to the degree of immaturity, is denied by other investigators (BAYER, BERNFELD). According to experiences from the premature department at Gothenburg, there is a remarkable tendency to oedema in the premature (v. SYDOW), which may

probably be associated with disturbances in the functioning of the capillaries and capillary endothelium. The great width which appears to characterize the liver capillaries in the premature, as also probably in those who have died of asphyxia during partus, is perhaps also an expression of a general susceptibility to capillary dilatation.

As a considerable degree of capillary dilatation is one of the fundamental changes in shock, it readily suggests itself to ask whether it is perhaps justifiable to speak of a disposition to shock in the new-born, especially in the premature. The data just mentioned seem to me to indicate this, and further facts which support that assumption may be adduced. As is well known, the red blood corpuscle picture in the full-term new-born immediately after partus exhibits a change in the direction of polyglobulia (VAHLQUIST, et al.). VAHLQUIST also showed that, in healthy full-term children, a difference between the red blood corpuscle content in the capillaries and veins could be proved. This difference disappeared at the age of 2 weeks. VAHLQUIST points out that this otherwise very unusual condition has only been observed in cases of shock. In principle the red blood corpuscle picture in the premature new-born is the same as in the full-term child (MAGNUSSON).

Hemoconcentration is an extremely characteristic symptom in cases of shock — according to MOON, it is the surest and often the earliest clinical sign of onsetting or threatened shock. Thus the data just adduced may be considered to indicate that there is a certain degree of disposition to shock in the full-term new-born also.

I will now return to the clinical picture which is often present in the premature and, as I have pointed out, tallies well with the assumption that in these cases it may be a question of shock. In the clinical literature I have only found one work dealing with shock in the new-born and/or premature, namely that by MILLER. He made thorough investigations of the blood chemism in the blood of the navel-cord in a number of new-born, among them a number of debile, and compared the data thus obtained with the child's condition after birth. He then found that hyper-

glycemia — but also hypoglycemia — decreased sodium value, hyperazotemia, and low values for the globulin fraction in blood serum, were more frequently associated with a poor or bad condition at or immediately after birth, than when normal values for the blood constituents in question were found. At the same time MILLER investigated the corresponding values in the mother's blood and considered that he found a certain correspondence between the values for the mother and the child. He did not work up his figures statistically. He divided the children according to their clinical condition after birth into four groups, namely, 1) those with normal reactions, who exhibited satisfactory respiration, colour and vitality within four minutes after birth, 2) those who required five to ten minutes to attain normal condition and thus reacted slowly, 3) those who needed between ten and twenty minutes' treatment, and who thus reacted extremely sluggishly, and finally, 4) the children who after twenty minutes still exhibited abnormal conditions. In the two last-mentioned groups Miller considered that shock was present.

As far as can be judged, the condition which MILLER here calls "shock" is identical with what is usually called "asphyxia in the new-born". In this paper I have already touched upon the question of the connection between asphyxia and anoxemia respectively, and shock. It might undoubtedly be asserted that an asphyctic condition may give rise to shock. In all probability, in cases of prolonged and severe asphyxia, e. g. of the asphyxia pallida type, a pronounced state of shock will be present.

In his work MILLER discusses, *inter alia*, the question of why some new-born who exhibited abnormal values for the blood constituents which were investigated, did not show any signs of shock. He says that no definite answer can be given to this question, but puts forward the suggestion that, besides the humoral factor, the blood change, great traumatization is necessary for shock to be manifest. The most striking finding in the majority of the premature comprised in MILLER's series was a great hypoglycemia. All those who had low blood-sugar values died within half an hour of birth.

With regard to the shock diagnosis in the new-born, MILLER

points out, *inter alia*, the limited value, in this connection, of a study of the pulse frequency and blood pressure in the new-born, especially owing to the technical difficulties. He also points out that, in view of the physiological conditions already mentioned, the hemoconcentration, as also the complicated hematological conditions during the "new-born period", make it extremely difficult, from a study of the state of the erythro-concentration and changes in it, to draw conclusions as regards the presence or absence of shock or disposition to shock. I have pointed out earlier that the hematological data in the healthy new-born speak to some extent in favour of a, so to speak, physiological disposition to shock.

It may perhaps seem that the question which is taken up here for discussion is of little or no practical importance and is of purely academic interest. I do not believe this to be the case, however. *Inter alia*, from the practical-therapeutic point of view, it will probably be of importance to attempt to elucidate as carefully as possible the pathogenesis of the disturbances met with in the premature. To the extent that these disturbances are the expression of shock, they should be subjected to suitable treatment. I shall not here go into the practical problems but will content myself with advancing a couple of points of view. A subnormal temperature is not only an ordinary symptom in cases of shock, but it can also give rise to shock. Experiences of the favourable effect which a sufficient supply of warmth has for the premature thus agrees well with the conception of a state of shock. The low temperatures which often characterize the premature, and which sometimes defy all treatment — as is well known an extremely ominous sign — are also in good agreement with the shock hypothesis. In cases of shock as in the premature, as far as can be judged, a supply of oxygen is beneficial, even when there is no clinical asphyxia.

In recent years suprarenal cortex preparations have been tried for the treatment of shock. Investigations, of which a more detailed account is given in MOON's monograph, have shown that the hormones of the suprarenal cortex are of great significance for the control of the permeability of the capillary endothelium. This has been proved, *inter alia*, by experiments on animals.

Clinically also, *inter alia*, in the case of burns, but above all prophylactically, e. g. before major surgical measures the use of a preparation of suprarenal cortex has been found to have definitely favourable effects.

In view of the importance which I have assumed that the mechanism of shock has for the appearance of a debilitated condition in the premature, therapeutic experiments with a suprarenal cortex preparation (cortin) have been made at the premature department here for some time. The first experiments were made on small premature babies, who already exhibited more or less serious symptoms, or at least signs of a none too good condition. After a supply of cortin by injection, it proved, almost without exception, that the effect was favourable. The most obvious expression of this was a more or less rosy colour of the skin, which succeeded the previous pale or ashen grey colour. The very experienced nurse in our premature department says that she is fully convinced of the effect. Most of the patients that have hitherto been treated in this manner had already for a more or less long time been lying in oxygen and had an ample supply of warmth, etc. — the whole of the usual therapeutic battery was in action. The only new feature was the cortin. In certain cases the effect was fairly lasting, in others it was more temporary. No undesirable secondary effects have been observed hitherto. Perhaps this may indicate that, if the favourable results continue, experiments should be made in giving cortin prophylactically to the least and less premature, for whom there is the greatest risk of serious disturbances.

### Summary.

The author discusses the conflicting opinions which, from the literature (e. g. YLPPÖ, PEIPER), appear to prevail in respect of the cause of death in the premature, or in the debile who die immediately after birth or during the "new-born period". The hypothesis is advanced that the low condition which often precedes death for a longer or shorter period, is a state of shock. The clinical picture tallies well with that typical of shock. As, for



various reasons, the special investigations usually made for the purpose of verifying the diagnosis of shock (e.g. examinations of the blood pressure and pulse, of changes in the erythrocyte concentration in the blood) cannot be employed in the case of the new-born and the premature, the author has tried to find support for the shock hypothesis in the anatomical findings. In autopsies on the premature the most typical and constant finding is a strong macroscopic and microscopic hyperaemia in the liver, and, usually, extremely wide intra-acinous capillaries. Other internal organs also exhibit at times, but by no means regularly, a certain, but generally not high degree of hyperaemia. Thus the anatomical findings appear to support the shock hypothesis. The physiological hemoconcentration which makes its appearance during the period immediately after birth in the full-term new-born — as also in the premature — speaks in favour of there being a special disposition to shock during the "new-born period". A number of anatomical data from the literature can also be adduced to support the assumption of a functional inferiority or deficient development of the capillary system in the premature, likely to favour the appearance of shock. Finally, a short description is given of some therapeutic experiments with suprarenal cortex hormone in cases of lowered conditions in the premature. These experiments have exhibited promising results and will be continued.

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The first of these is the fact that the United States is a young nation. It is only about 150 years old, and its history is therefore a history of rapid growth and change. The second is the fact that the United States is a large nation. It covers a vast area of land, and its population is one of the largest in the world. The third is the fact that the United States is a diverse nation. It is made up of many different peoples, races, and religions, and this diversity has been one of its strengths.

The fourth is the fact that the United States is a nation of immigrants. Many of the people who live in the United States today are the descendants of immigrants from other countries. This has helped to make the United States a more tolerant and accepting nation. The fifth is the fact that the United States is a nation of pioneers. The people who first settled in the United States were pioneers, and they have left a legacy of courage and adventure.

